Cold Spray as an emerging technology for biocompatible and antibacterial coatings: State of Art

A.M.Vilardell*, N.Cinca, A.Concustell, S.Dosta, I.G.Cano, J.M.Guilemany

1. Introduction

The massive increase in human aging has affected different areas such as economical, social and health, especially the last one, with the increase of chronic diseases. It is anticipated that elderly people (+65 years) will reach up to 20% of European population in 2050, compared with the 10% of nowadays [1]. For centuries a diseased tissue was removed to improve marginally the quality of life. With the scientific advances in biomedical field however, it has led to an increase in human survivability aversely to the quality of tissues, thus the arising need to replace tissues [2]. In terms of orthopaedics, more and more patients will require the use of prostheses in order to replace critical parts of the skeletal system.

Current patients complaint about conventional prostheses include: (i) socket-related problems of discomfort, sores, rashes, and pain, (ii) the difficulties on donning the prosthesis, (iii) the unreliability of prosthesis being securely suspended and, (iv) mobility difficulties. While innovation on new materials with better mechanical and biological properties is day by day carried out through the collaboration of many scientific disciplines, the osteointegration by the surface modification of conventional prosthetic materials can still offer many possibilities for the improvement of bone reabsortion decreasing the allergenic response. In addition, in many cases, the surgery for prosthesis replacement is extremely aggressive and the cost is high; therefore, whatever solution that can extend the prosthesis life will be very welcome by clinical community.

The biomaterials field is always under development and has experienced considerable progress especially over the last 60-70 years [3,4]. The definition of a biomaterial, currently proposed as “a non-viable material, used in a medical device, intended to interact with biological systems” was definitely established by William D.F in 1987 [5]. The development of biomaterials for medical applications has evolved through three generations, each with a distinct objective (Fig.1). Specific familiar terms such as bioinert, bioactive or biodegradable allow their classification according to their characteristics within the body.

Bioactive materials are an intermediate between resorbable and bioinert (Fig.2) [6]. The first denoted bioactive material was Bioglass®, also known as 45S5 bioactive glass in the late 1960s by Larry Hench [7] and the concept of using synthetic resorbable ceramics as bone substitutes was introduced in 1969 [8] then hydroxyapatite (HA) as well as some other glass-ceramics appeared within the market circa 1985s [9,10]. Bioactive materials are classified in two categories: (i) Osteoproductive materials, that are recognized by the intracellular and extracellular responses elicited at their interfaces (e.g Bioglasses) whereas, (ii) Osteoconductive materials only elicit an extracellular response at their interfaces (e.g. Hydroxyapatite). Bioglasses induce integration between bone and implant in the form of a continuous interfacial layer, while osteoconductivity only induces bone growth directly at the implant surface and often results in a fibrous capsule between the implant surface and bone.

The two primary issues in biomaterials are: biocompatibility and structural compatibility [11]. Considering the biocompatibility as “the ability of a material to perform with an appropriate host response in a specific application” [5], it implicitly refers two terms: biosafety and biostability, where the material does not have to provoke chronic inflammation/infection that may cause cell death or produce a disfunction in cellular and tissue matrix [12]. Structural compatibility refers to mechanical properties and becomes especially important for prosthesis biomaterials.

Surface characteristics such roughness [13] and porosity [14] influence cell attachment and promote bond in growth fixation between implant and host issues due to its structure and free surface. The concept of bioactivity is actually highly related with those characteristics, which will be many times addressed along this paper.

1.1. Surface treatments and biocompatible coatings: current status

Surface engineering has helped to biomedical science to provide better understanding of implant-tissue interactions; the surface modification methods include both, the chemical modification and surface roughness as well. The atoms on the surface are more prompt to undergo phase transformations, crystallization or corrosion (dissolution) processes; this higher energy and higher reactivity are particularly important in view of adsorbates from the biological system. Cellular activity, protein adsorption or tissue response has been specially induced in titanium-based alloys by surface roughening, acid treatment, anodization and coating techniques i.e. thermal spraying, etc., methods that produce surface topography changes mainly at the microscale level [15]. Other attempts to improve osteoblast activity include the promotion of surface roughness with combined micrometer and nanometer structures such as photo, electron beam and colloidal lithography or electrochemical anodisation [12,16].

Concerning metal coatings, Vacuum Plasma Spraying (VPS) is, for example, widely used to prepare rough and porous titanium coatings [17- 21]. Yang et al. [17] obtained titanium (Ti) coatings on Ti substrates consisting of an outer layer full of macropores with a surface roughness of approximately Ra=100 µm (such macropores are reported to be beneficial for tissue ingrowth into the coating), a middle layer consisting of a mixture of micropores and macropores and, an inner dense layer. By contrast however, Borsari et al. [19] used the same technique to produce rough but dense VPS-Ti coatings with the purpose of avoiding as much the reduction in bone density, also known as “stress shielding”, as possible, and thus prolong the prosthesis lifespan. The aim of that study was to investigate the in vitro effect of high roughness (Ra=73.75 µm) and dense Ti surface in comparison with medium (Ra=18.42 µm) and high roughness (Ra=39.64 µm) and open porous coatings. Such new ultra-high rough and dense VPS coating provided a good biological response; at least in vitro, it behaved similarly to the coatings already used in orthopedics. The effect of the coating stability and ultra-high roughness level after surgical implantation and during dynamic bone healing and remodelling has yet to be established. Other titanium coatings for medical devices include, open-porosity, porosity, mixtures of bioactive feedstock powders materials.

Other Thermal Spray (TS) metal coatings attempts include tantalum (Ta) and silver (Ag). Tantalum coatings have an excellent corrosion, good formability, low coefficient of expansion, excellent wear resistance and excellent biocompatibility and radio-opacity for biomedical applications. Recent in vitro, in vivo, and clinical studies demonstrated that tantalum is a promising bioactive metal [22,23]. Since tantalum applications in biomedical devices have been limited by processing challenges rather than biological performance, Ta coatings have been achieved via Plasma Spray (APS) and High Velocity Oxy Fuel (HVOF). Optimizing spraying parameters lead to minimum porosity and oxide content but without good corrosion protection [22,23]; in addition, there are still some drawbacks such the high cost and the high reactivity at temperatures above 500ºC where oxidation causes loss of ductility and cracking of the surface material. Other coating methods by which tantalum has been deposited include LENS™ (Laser Engineered Net Shaping) [24], sputter deposition [25], chemical vapor deposition (CVD) and electrodeposition.

From another hand, silver has been highlight since ancient times for its antibacterial, antifungal and antiviral properties; also its compounds such as silver nitrate and silver sulfadiazine, have been used for the treatment of burns, wounds and several bacterial infections [26-28]. Pure silver coatings by different methodologies have been tested with very good results, especially in catheters [29-34]. Using thermal spray methods however, silver has been codeposited with many other materials [35-39]. For example, Hydroxyapatite/Silver composite coatings obtained via VPS proved to combine antibacterial and bioactivity properties; it was found non cytotoxicity for the coatings and they were covered by bone-like apatite layer after immersed in Simulated Body Fluids (SBF), suggesting that their bioactivity was not affected obviously by the addition of silver in the coatings [40].

Concerning ceramic coatings, plasma sprayed alumina and zirconia are being used clinically, mostly due to their higher wear resistance than titania. However, alumina and zirconia coatings cannot bind directly to bone tissues due to their bio-inert nature, thus limiting their use in hard tissue applications. Moreover, there is a controversy on the binding strength and on particle release from plasma sprayed coatings into the host tissue, caused by either dissolution or fretting. Therefore, the use of bioactive hydroxyapatite (HA) coatings produced by plasma spraying (APS) [41-44], high velocity oxy-fuel (HVOF) [45-47] and flame spray as well [48] was a very successful achievement; in HVOF, particles reach lower temperatures and higher velocities that minimize the time of residence of the particles within the spray beam and therefore its thermal decomposition [1,49]. HA-coated prosthesis maximize fixation and decrease the migration of microparticles along the prostheses [50]; they are a good alternative to cemented prosthesis, which have high rates of loosening. In addition, Chern et al. [51] compared the coating-substrate bonding strength of HA with other bioactive coatings such as bioglass, bioglass-HA and found that bonding strength was 33,0±4,3, 39,1±5,0, 52±11,7 MPa for bioglass, bioglass-HA and HAcoatings respectively. It was demonstrated that after 4 weeks bone ingrowth was significantly higher in bioglass and

HA coatings but after 16 weeks only bioglass maintained its highs percentages of bone ingrowth while in HA decreased with time [52]. Despite having excellent bioactivity, the mechanical properties of bioactive glasses are worse than bioactive HA; this problem can be solved by combining those bioactive materials with metals or polymers to produce a composite coating surface [53]. Cai et al. [54] developed a sintered Co-Cr-Mo/Bioglass composite coating for medical implant application in order to be compared to plasma sprayed coatings. Those coatings show a more porous structure than plasma spray but less wear resistance. Nevertheless, an adequate bonding between Co-Cr-Mo/Bioglass composite coating was achieved and furthermore a apatite layer on top of the coating performed bioactivity. Moreover, more processes are used to fabricate composite bioglass coatings, such as sol-gel[55], electrophoeric deposition [56] and pulsed laser deposition [57].

Even enhanced biocompatibilities are achieved by using nanocrystalline ceramics [58,59]. HA particles shape has a high influence in cells performance (e.g: needle shaped particles promote inflammatory reaction, spherical shaped particles show increase inhibition with time and concentration of those in U2-OS cancer cells, and irregular shaped particles produced a greater response than spherical shaped particles).

However, there is still some concern about the uniformity, the adherence of the coatings and the dissolution rates due to crystalline issues affecting long-term stability. The lack of uniformity is related to the uncontrollable crystallinity within HA plasma coatings, leading to many different phases such as alpha tricalcium phosphate (α-TCP), beta tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), Oxyapatite (OHA) and amorphous phases (ACP), whereas the concern on the adherence is attributed to the presence of amorphous phases at the coating-substrate interface. Ceramic bond coats based on zirconia and titania have been plasma sprayed in order to be employed to act as chemical barrier against in vivo release of metal ions from the implant and improve the adhesive bond [60]. Table 1 includes the requirements of HA coatings for implants for surgery specified by different ISO and ASTM standards [61-65].

Other coating technologies have also been employed for the production of HA coatings but compared to thermal spray processes (TS) are less cost-effective. Table 2 shows some advantages and disadvantages of TS compared to such other possibilities.

Some other variations of these type of coatings have been performed such as by using HA-TiO_2 mixtures to improve mechanical properties i.e. bond strength, fracture toughness and wear resistance [70-72], fluoroapatite-HA mixtures given that fluorapatite offers the potential for lower mineral ion release by dissolution [73], yttria stabilized zirconia reinforced HA/Ti–6Al–4V composites which leads to significantly higher mechanical properties than pure HA coatings (even after immersion in SBF solution) [74], Ta/HA layers to improve the corrosion resistance and biocompatibility [75], Ag-HA mixtures to reduce bacterial adhesion [76-78] or by using carbon-nanotube reinforcement imparting strength and toughness to brittle HA bioceramic coating [79].

All these surface modifications have been developed over the past decades to improve the bioactivity mostly of Ti-based implants and its bonding strength to the host tissue. However, although many research groups are still working on this topic, there has been more recently an upgrade on the study of polymer composite materials as an alternative choice to overcome the shortcomings of metals and ceramics [4]. The poly(ether ether ketone) (PEEK), for example, highlights for its biocompatibility, bioinertness and similar elastic modulus to the bone and, their good mechanical properties for hard tissue applications (hip and knee replacements) [80]; other polymers such as Poly(lactic acid) PLA -bone plates, tendons and ligaments- and poly-L-lactide (PLLA) -bone plates- stand out for their fully resorbable property; Polyurethane (PU) and Silicone Rubber (SR) get distinguish because of their flexibility in catheters. Some of the attempts to improve the bioactivity of these polymers include coating with tantalum [81], gold, titanium dioxide (TiO_2), diamond-like carbon (DLC), and tert-butoxides [82].

The bioactivity requirement, depending on the component application, can be also pursued by proper manufacturing routes [83]. In this direction, some researchers have developed human hip joint prosthesis made of fiber reinforced poly(ether ether ketone) (CF/PEEK) and coated the stem with Vacuum Plasma Sprayed (VPS) Ti/HA coatings [84]; the mechanical tests of the prosthesis produced by Riner et al. indicated good long term stability of the bone-prosthesis system, while the in-vitro and in-vivo tests proved no cytotoxicity and necrotic effects in rabbits. Apart from plasma spraying, HA coatings have been also produced on PEEK substrates by other processes such as RF magnetron sputtering and aerosol technique.

1.2. Biocoatings market for orthopaedic implant with focus on thermal spray

As schemed in figure 1, after the first generation of load-bearing implants (cortical bone substitution) by using bioinert materials (stainless steel 316L, cobalt chromium alloy, titanium, or titanium alloy (Ti-6%Al-4%V)), the second generation involving surface treatments, emerged prominently in 1985 with the first HA-coated femoral prosthesis (Furlong®, JRI, London, UK) [85]. In general, in-vitro and in-vivo studies indicate that bioactive biomaterials application in biomedical field increase the long-term durability of prostheses. Since first clinical reported trials of HA coatings on femoral stems, HA coatings were extensively used in dental and orthopedic prosthesis [86]. HA coatings are currently being used in total hip [87,88] and knee [89] replacement implants, ankle and shoulder implants, screws and pins in bone plates for fixing bone fractures. Medical studies were done such acetabular cups in total hip arthoplasty [90] and tibial component in total knee arthoplasty [91] at a minimum duration of follow-up of five years comparing different fixations, like HA coatings, porous surfaces and cemented fixations. HA-coatings surfaces stabilized after an initial period of early migration, whereas cemented components showed an initially lower, but over time continuously increasing migration. Some of biomaterials used in skeletal system applications are shown in table 3 together with medical market.

At the moment, some of the successful bioactive coatings for implants have been produced by electrodeposition and plasma spraying: Peri-apatite™, Biomet's Osteocoat® , Corail® , among the most important. Other successful approaches have been: (i) the development of a macro-sized interconnected porosity in the range of 100-500 µm within a metal coating with the aim to promote proper bone ingrowth i.e. Regenerex™, Trabecular Metal™, Arcam AB Trabecular Structures™ and (ii) nanoscale topographies i.e. OsseoSpeed™ , Nanotite™. Table 4 presents some of the characteristics of the current commercial orthopedic implants [92].

2. Thermal spray processes

2.1. Conventional technologies

TS is a group of techniques to produce metallic and non-metallic coatings where the feedstock is sprayed in molten or semimolten state onto a prepared substrate. Their basic principle is to impart sufficient kinetic and thermal energy to the raw material (in powder, wire or rod form) to create a confined high-energy particle stream, and propel the energetic particles toward the substrate. Through the solidification of the droplets on impact with the substrate, they create cohesive bonds with each other and adhesive bonds with the substrate; many different spraying parameters need to be optimized to produce suitable coatings for the desired applications (Fig. 3).

The particles are heated by electrical (air plasma or arc wire spraying) or chemical (detonation gun, flame spraying or high velocity oxy fuel) means. Droplets impact and start bonding onto substrate due to high cooling rate, typically excess of 10^6K/s for metals [93-95]. Coating properties directly depend on particle temperatures and speeds, which produce thin layers o lamellas, often, called “Splats”, that finally buildup the deposit. There are three types of bonding mechanisms at interface substrate-coating, being predominant the mechanical bonding followed by metallurgical ones [95]:

- Mechanical bonding, particles, molten or semi-molten, impact onto surface substrate (previously grit-blasted) and remain adhered due to its roughness.

- Metallurgical bonding, given by the occurrence of interdifusion processes between substrate-coating and even though the formation one new compounds such as intermetallic phases.

- Physical bonding, reached by Van deer Waals forces between substrate-coat.

Thermal Spraying techniques are divided in three subgroups according to the energy source (Fig.4) and the selection of the appropriate spraying method will be determined by: coating material characteristics, coating performance requirements, economics and, part size and portability.

2.1.1. Advantages of conventional technologies

A big advantage of thermal spray processes is the ability to deposit an extremely wide range of materials. Virtually any material that has a stable molten phase can be deposited, and even some materials that do not melt, such as graphite and many carbide or boride ceramics, can often be co-deposited with another sprayable material to create a composite coating material. Another one is that the range of suitable substrate materials is even greater that the range of sprayable materials. In addition to metals, ceramics, glasses, and polymers, thermal spray coatings have been successfully applied to many other substrate materials including wood. Conventional thermal spray also offers the advantage of high deposition rates, which are orders of magnitude higher than those of most alternative coating technologies, such as electroplating or vapor deposition, where deposition occurs at the atomic or molecular level. When the objects to be coated are very large or difficult to move, the ability to apply coating is in-situ, is also an advantage. Furthermore, coatings can be applied without significant heat input and it is possible to strip off and recoat worn or damaged coatings without changing part properties or dimensions. Further advantages of Thermal Spraying include its rapid coating deposition, low-cost, high efficiency and rapid execution process.

Although all the techniques exposed in table 2 are suitable to produce bioactive HA layers, only thermal spraying, in particular, plasma spraying is the commercially accepted method by Food and Drug Administration (FDA), USA for producing hydroxyapatite coatings [96].

2.1.2. Limitations of conventional technologies

TS deposition features depend on the used technique and, the thermal and kinetic applied energy will be different. High temperatures cause oxide inclusions (overcoat metallic materials) as well as decomposition/degradation in oxygen-sensitive materials such titanium or HA respectively. Oxide inclusions improve mechanical properties like wear resistance and hardness, but an excessive presence at intersplat regions lead to cohesive failure and wear debris [97]. Processes that minimize heating of the spray material, such as HVOF and D-Gun, typically result in lower oxide concentration and minimal changes in alloy chemistry. Also, the controlled inert atmosphere of VPS creates very little or no oxide during the deposition process; however, some changes in the alloy chemistry may still occur due to relatively high temperatures in the plasma jet. High porosity could be beneficial in some applications like in the case of prosthesis to promote a good bone ingrowth; conversely, excessive porosity can also be a problem if the coating is intended to protect the underlying substrate from species that can cause corrosion or other problems. Porosity depends more over on size particle distribution and spray distance, producing “unmelted” particles according to their inertia when are fed into the plume. Also, low-velocity processes tend to have higher level of porosity in the range of 5-15% volume, and higher velocity processes origin coatings with less porosity (3-8% volume). Another limitation is the introduction of residual stresses that limits the maximum thickness due to the solidification of droplets when they cool down

[98]. Finally, the deposition is limited to surfaces in a direct line-of-sight of the spray gun.

Cold Spray (CS), a novel spray technique in the late of 1980s, mainly arises from the limitations of some coating types of thermal spray that seem to be overcome for some materials. CS is a low-temperature process based on the plastic deformation of the spraying material and it is suitable for the deposition of oxygen-sensitive materials, or for temperature sensitive materials like nanostructured and amorphous powders [97-100]. Moreover, it should also be noticed that, compared to the conventional thermal spray technologies and other coating alternatives like painting and electrodeposition, cold spray is an environmental friendly approach since its effluents are easy to control and to dispose and it is a non-combustion process.

2.2. Cold Spray technique

Cold Spray (CS) is newest recent spray technology from the thermal spray family from 1980s; it is based on the kinetics energy and stands above conventional spray techniques for its low temperature rates. Small particles (5-50μm) are accelerated by a pre-heated gas temperature (25-1100ºC) lower than the melting point of the material and propelled towards a prepared substrate at supersonic velocities (300-1200m/s). Supersonic flows from gas dynamics are obtained within nozzle with the principal purpose to maximize the thrust and obtain a better coating quality. Nozzle design influences on particle velocity, depending basically on the type of nozzle and its geometry. From the three basic nozzles: Convergent-barrel (CB nozzle), convergent-divergent (CD nozzle) and convergent-divergent-barrel (CDB nozzle), the one who achieves a higher particle velocity is CD nozzles, known also as Laval nozzle with its conical geometry.

Particle binding is made by kinetics energy when particle impacts onto a surface causing plastically deformation [98], becoming particle velocity an important parameter. Due to high kinetics, CS is able to produce quality dense coatings. However, depending on spraying conditions a particle size, it is able to obtain porous coatings. Figure 5 shows a schema of CS technique.

Instantly, the feedstock located in the feeder is propelled by gas (normally N_2), and pre-heated gas (N_2, Air or helium) at determinate temperature and pressure, into the spray nozzle, to propel particles at high velocities to buildup the coating. Stages of coating formation are shown in figure 6 [101].

2.2.1. Advantages of CS technology

The main advantage of the cold spray process is that it is a solid-state process, which results in many unique coating characteristics. High deposition efficiency values have been achieved with metals, alloys and composites; high deposition rates can produce a thick coating in a single pass (1-2mm) due to its typical spray beam of about 10mm of diameter [98].

CS can be viewed as a triplex process (grit blast, spray coat and shot peen), as is to be expected caused by the velocity Gaussian distribution across the spray beam; flexibility in substrate-coating selection is good to produce coatings that could lead to unacceptable interfaces in APS or HVOF that i.e intermetallic phases between Cu-Al with APS; minimum thermal input to the substrate facilitates the use of temperature and oxygen sensitive materials such magnesium, titanium and polymers. Moreover, residual tensile thermal stresses remain in a TS coating produced by a conventional process, whereas CS induce stresses mostly in compressive nature across the entire coating thickness, which improves mechanical properties such as fatigue. However, some investigations confirm that in specific cases neutral and tensile stresses may appear depending on substrate/coating combination and surface treatment. Suhoen et al. [102] deposited Al, Ti and Cu onto carbon steel (CS), SS and Al substrates with different surface treatments. It has been shown that compressive residual stresses predominate in Cu deposition onto the majority of the specimens; also Ti coatings may show compressive, neutral or tensile residual stresses depending on the substrate; by contrast, Al coatings exhibited tensile residual stresses onto all the substrates.

Furthermore, compressive residual stresses may be detrimental if relatively thick coatings are sprayed onto thin substrates and they produce their deformation; also, they have to be taken into account in the case that they promote tensile stresses to the substrate. Therefore, residual stresses should be considered in any application where structures are required to carry load.

It has been demonstrated that metals, polymers, ceramics and composite materials are able to be applied with CS technology in a wide range of applications that are in constant development, such as those involving corrosion protection, repairing structures, catalyst deposition, electromagnet transition, electronic and medical devices [103,104].

Depending on spraying materials properties, grid blasting could be a good option to improve particle attachment onto substrate if a mechanical anchoring effect contributes in the bonding mechanism [105,106,107]. However, it might be detrimental if this induces hardening of the substrate surface since it would change the mechanical surface characteristics [108,109,110].

2.2.2. Process parameters of CS technology

The actual mechanism by which the solid particles deform and bond during CS is still not well understood. Particles undergo to an extensive plastic deformation when impact onto the substrate, which results in the creation of jets, known as Adiabatic Shear Bands (ASB), in the case of ductile materials such metals. It is believed that the contact of substrate surface and particle with the high pressures is necessary for particle bonding. Actually, for metals which are the mostly deposited materials by CS, the resulting microstructure resembles to that of a cold worked material, with elongated grains and even recrystallized areas at particle interfaces where a higher temperature is reached a result of adiabatic shearing [111]; such microstructures have been well compared to those of powder compacted and explosive welded materials. A wide range of ductile materials (metallic and polymeric) have been successfully deposited by CS, whereas non-ductile materials such as ceramics are able to deposit onto ductile substrates where particle could be embedded.

Generally, for each material, there is a critical velocity (Vc) for its successful deposition onto a certain substrate. Only those particles that exceed this critical velocity (Vp>Vc) will be successfully deposited to build up a coating, but higher impact velocities may results in erosion of surface substrate.

This critical velocity depends, from one side, on the intrinsic characteristics of the spraying material i.e. the physical and mechanical properties such as density, melting point and ultimate strength and, from another side on the particle size, morphology, temperature and substrate; in addition, the particle velocity (Vp) also depends on the spray gun parameters i.e gas composition, gas preheat temperature, gas pressure and nozzle geometry. An optimization of all these parameters is many times critical for a good deposition [100].

Metal, cermet and polymeric coatings have been successfully produced onto different substrates, but ceramic coatings are still a challenge due to its intrinsic brittleness. Blends of metal-ceramic feedstock powders have been sprayed by CS leading to improved coating properties such wear and hardness [112]; as it will be later discussed, this alternative has been successfully used to produce titanium-HA coatings.

3. Biocoatings via CS

3.1. Metal biocoatings

Biocompatible metals were the first family of materials to be sprayed via CS within this field due to their high plasticities and thus the feasibility to produce coatings with good efficiencies. The first metal coatings that were used for biomedical applications were of Stainless Steel (SS) and titanium. In analogy to porous plasma sprayed titanium coatings, these have been also produced by CS with the aim to allow bone in-growth.

By changing the spraying conditions, it is posible to reach different porosity levels. Li et al. [113] presented the microstructure of cold sprayed Ti and Ti6Al4V coatings onto Ti6Al4V substrates and the effect of heat treatment on coating microstructure. These authors achieved an average porosity of 5,4±2,4% and 22,3±4,7% before the heat treatment; after the heat treatment, the porosity increased to 21,6±4,6% and 29,7±5,1% probably by the healing of the incomplete interfaces through the atom diffusion during annealing treatment. In addition, Wong et al. is another example of how the authors achieve different degrees of porosity by a wide range of modification of the spraying conditions (Fig.7) [114]. It might be also worth noting that the density of the microstructure can be influenced by the tamping effect, this is the successive impact of following particles, therefore leading to more porous structures on the top rather than near the interface with the substrate [115].

On the other hand, some authors have used materials such as magnesium or aluminum to produce porosity. Sun et al. [116] produced porous titanium coatings spraying Mg+Ti powders onto titanium, where the magnesium behaved as space holder and is eliminated by vacuum sintering. Plasma sprayed porous titanium coatings usually exhibit irregular porosity distribution and the pores are not well interconnected, while other methods such as sintering titanium beads or fibers have relatively low porosity (<37%) and low cohesive and/or bond strength. By contrast, CS coatings by Mg+Ti resulted in an average porosity of 48,6% and pore sizes in the range of 70 to 150µm. Bending modulus and compressive modulus of porous titanium coating were close to the bone and thus may be beneficial to reducing stress shielding. Qiu et al. used aluminum as porogen to form porous titanium coatings [117], which was removed after spraying by alkaline leaching. Considering all test, the average pore size was between 74-91µm and the pore percentage between 48-66%.. Figure 8 shows the porous morphologies and cross section of both studies with pore sizes of 50-150 µm and 70-150 µm respectively.

Furthermore, well-adhered, thick and homogeneous titanium coatings have been also produced onto PEEK biopolymer without its degradation, with the aim to enhance PEEKs biocompatibility for implant applications [118]. This responds to the new emerging use of PEEK as a novel alternative within the biomedical field. Table 5 shows the CS Spray conditions of metal coatings used for biocoatings. Spraying onto UHMWPE has also been produced with the aim to avoid having the polyethylene liner and the acetabular cup as two separate components. In such a way, the rough titanium shell and the polymer contacting the femoral head can be achieved within the same component; this was obtained through properly surface activation previous to spraying [119].

The ability to produce refined-grain coatings via CS, due to unchanged microstructure of the feedstock powder material, has been also taken benefit in the biomedical field, specifically in coronary stents. AL-Mangour et al. [120] performed mechanical and corrosion properties in stents coated by a mixture of L605 cobalt-chromium (Co-Cr) alloy and 316-L SS onto mild steel, where it was observed that the addition of cobalt powders helped to obtain dense coatings. A heat treatment improved then the densification and porosity reduction as well as a significant increase of ductility; also, despite in vivo and in vitro tests are still pending, the Co-Cr alloy showed a lower corrosion rate than pure SS, making it suitable for the development of a new class of metallic biomaterials.

Other attempts were done with Tantalum (Ta). Cold Spray (CS), as it works with low temperatures, is being studies for produce Ta coatings where it is observed good interface adhesion, low porosity and increase of hardness [121].

Finally, metal coatings have also been produced by CS for bone fracture fixation systems in order to prevent bonding or one or more types of corrosion between the metallic fastener and the metallic bone plate [122]. Where the components of an internal fixation device subsequently bond together, the surgeon may have extreme difficultly disengaging one component from the other, such as disengaging a bone screw from within an opening in a bone plate. The bonding may prevent the separation of the components and therefore, it can result in injuries due to the prevention of the components being removed from the patient. This patented procedure comprises a cold-sprayed metallic coating either within the opening or on the metallic fastener. The cold-sprayed metallic coating comprises a biocompatible metallic material having a third composition that is different than the first and second compositions.

3.2. Ceramic-based biocoatings

Specifically, bioactive ceramic coatings highlight for their direct bond to living tissues when implanted. Looking for fixation, bioactive fixation forms a bond with higher strength than mechanical fixation. Nevertheless, TiO_2 coatings are currently been investigate by CGS despite its good mechanical properties and biocompatibility. Kilemann et al. [123] studied the formation of TiO_2 particles onto metallic substrates. TiO_2 particles interact as solid spheres with the substrate bonding in a ring-like zone. Particles breaks into small remnants remain in the bonding zones. Only if substrate material is brought to the surface and is available to bind other particles, a second layer or parts of it are likely to be attached to the coating on impact. Salim et al. [124] sprayed a novel synthesis of TiO_2 powders for CS in which makes it possible the deposition of those particles by CS and the growing up of a layer without the addition of binder, but onto Cu not in biocompatible material. Nevertheless, investigations are currently running out.

3.2.1. HA biocoatings

Previously, the advantages of CS over conventional thermal spray processes have been mainly associated to high temperature-related features. HA coatings have been found to promote fast and enhanced fixation strength but the long-term stability of the fixation has been reported to still be a challenge in TS techniques; for this main reason CS is proposed as an alternative to produce HA coatings with high density and controlled crystallinity. In front of other low-temperature processes such as sol-gel, biomimetic deposition, solution deposition, electrochemical deposition and atomic layer deposition, HA cold spray technique highlights for its simple and economic process of producing coatings at low temperatures being able to control coatings microstructure.

Despite the common sense that HA particles bombardment is like blasting the metal surface of the implant, some approaches have been done in this direction [125-129] and even more successful by dealing with a shot-penning route [130]. Cold Gas Spray of ceramics has been actually compared to other low temperature powder-based dry manufacturing processes i.e. aerosol deposition (AD), sometimes known as vacuum cold spray (VCS) and nano-particle deposition system (NPDS), which appeared in the 1990s and 2000s respectively. AD is based on the acceleration of submicrometer particles but low-vacuum conditions are necessary to control the supersonic flow. In NPDS, the source of bonding is attributed to the dissipation of the kinetic energy of the particles. The use of submicrometer feedstock particles seems to be also important and some plasticity features have been revealed [131-133]. Dense hydroxyapatite coatings have been deposited on titanium by this method [134-135].

Different numerical and simulation studies have been developed to come upon optimal conditions for cold spraying of spraying HA. Zhang et al. [136] studied the factors influencing HA particle acceleration using a computational fluid dynamics program FLUENT. The simulation results showed that the HA particle is accelerated by the combination of throat diameter and exit diameter whose expansion ratios lie within the optimal range of 1.5-4. HA particle velocity increases with the increasing of gas pressure notably from 0.2MPA (150mm/s) at 0.6MPa (360mm/s) and with the decrease of HA particle size until a minimum of 5μm, where it decelerates steeply, being 5-20μm size particle suitable for spray with CS. the taguchi method, was used by Singh [137] to optimize HA conditions in CS; they calculated the percentage contribution of all factors on exit particle velocity of HA powder, being as follows in descending order: Gas Type>Particle Diameter>Gas Inlet Pressure>Particle Temperature>Gas Inlet Temperature. Moreover, they observed the combination of those parameters can alter the result [138]; the increase of gas pressure and particle temperature was found to increase the particle velocity, while the increase of HA particle diameter was found to decrease the particle velocity and its influence was found to be more than respective influences of gas pressure, gas temperature and particle temperature. Therefore, HA particle velocity is inversely proportional to particle size, despite the increase of gas pressure and gas temperature.

Recent investigations concern biodegradable implants and biocompatible coatings on implant materials for example magnesium-based alloys. Despite its excellent properties magnesium-based alloys have not seen tangible applications in biomedical field industry. To date they have been studied within the development of cardiovascular stents, bone fixation material and porous scaffolds for bone repair. Nevertheless, the main limitation to the medical application is their rapidly and localized corrosion behavior. In order to control the degradation rates, it is useful to coat with HA. APS studies have not been developed for its high temperatures that could melt magnesium substrate and decompose HA in other calcium phosphate phases and the crystallinity of HA may also be lowered due to rapid solidifications. CS has offered solution to both problems [139].

On another hand, pure HA coatings have been produced on PEEK substrates by CS, therefore providing bioactivity to a material that avoids the stress shielding phenomenon normally occurring between a metallic material and the bone and, the weak mechanical properties of ceramic substrates [140]. Coating polymeric biomaterials with calcium phosphate is also one of the most effective methods to enhance biocompatibility. However, calcium phosphate ceramic coatings necessitate a heat treatment at a high temperature in order to induce crystallization of the coating layer, or necessitate a cost-consuming vacuum deposition method for low temperature crystallization in order to control/obtain other calcium phosphate phases. In the case of polymeric biomaterials, a heat treatment at a high temperature brings about deformation of polymers, and such deformation eventually deteriorates the performance of polymers, preventing the polymers from being used as biomaterials. Furthermore, a vacuum deposition method at a low temperature may also damage the surfaces of polymers, causing deformation, and requires high production cost to increase productivity, which is not preferable. CS overcomes the limitations of various conventional coating methods, and enables coating of the surfaces of polymeric biomaterials while maintaining the intrinsic properties of both the powder and the polymer, with low production cost and high productivity. This patent includes as bioactive coatings HA, bioglass compounds such as bioglasses containing CaO, SiO_2 and P_2O_5 as main ingredients, and crystallized bioglasses; and mixtures thereof [140]. Lee et al. [141] also evaluated the bioactivity of HA coatings on PEEK substrates by CS; these proved to be homogeneous and strongly adhered without any deformation of the substrate material.

3.2.2. HA-composite biocoatings

Due to the intrinsic brittle nature of ceramics, a direct deposition of a uniform layer with proper adhesion is still a challenge via CS, specially onto the typical metallic prosthesis i.e titanium and SS, on account of the inelastic deformation that ends in failure fragmentation. This has already been observed by the few studies reported in the previous section. For a better understanding of this behavior, lots of studies are being carried out on the investigation of failure mechanisms of ceramics at dynamic impacts [142,143].Significant efforts are thus addressed in the direction of using metal-ceramic and polymer-ceramic composite powders. Some works deal with HA-Ti mixtures [144,145]. The results showed that compared to pure Ti coating, cold sprayed HA/Ti composite coating exhibits higher corrosion current and lower corrosion resistance. However, a post spray heat treatment can improve the corrosion property of HA/Ti composite coating remarkably. In addition, the mechanical properties such as microhardness and ultimate shear strength of cold sprayed 20wt% HAP/Ti composite coating also improved up to three times by a post spray heat treatment process. Further, the recrystallization also favoured the interfacial bonding and hence improved the mechanical properties [146]. Choudhuri et al. [147] also demonstrated that HA-Ti mixture powders can be cold sprayed achieving a better bond strength (24.45MPa) than APS (~10-15MPa); two different titanium powders were used in those mixtures: a vacuum atomized commercial pure Ti (Cp-Ti) and a sponge titanium powder both from a particle size ~45µm.

Cp-Ti showed difficulties to build up the coating by encapsulating HA particles, whereas the use of sponge Ti powder was more effective. The maximum incorporation of HA was of a 20%; above that percentage, it was found that HA particles got crushed into fragments due to high impacts.

As reported before, aluminum powders have been used as a porogen, in combination with titanium, to achieve porous titanium coatings with higher interconnected macroporosity and larger specific surface area; in order to make these coatings bioactive, HA was added to facilitate bone cell attachment and ingrowth, leading to outstanding in-vitro HA mineralization, although long term studies are required [117]. Such authors used two types of HA, a crystalline and an amorphous calcium phosphate nanocrystalline HA (NC-HA) were it could be observed that NC-HA reach a maximum Ca^{2+} mineralization efficiency promoting an early bone fixation.

Other attempts, in that case of cold-sprayed HA-composite coatings include: HA-graphene nanohseet (GN) [148], with the aim to avoid the concerns related to its long-term performance, i.e., the intrinsic brittleness and low fracture toughness of HA and, doping HA with silver [149], with the advantages that silver involve. The addition of graphene has been proved to be very suitable for load-bearing applications, exhibiting a very reasonable biocompatibility as well; it was even embedded in HA matrix and plastic deformation of certain nano HA particles was revealed. The GN-containing HA coatings markedly enhanced attachment and proliferation of the osteoblast cells, which is most likely attributed to fast adsorption of key serum proteins like fibronectin with elongated stretching conformation on GN. Table 6 shows different cases CS conditions for biomedical applications.

4. Clinical performance

This is a very novel topic and since many few researchers have optimized their coating systems, not many in-vitro and in-vivo results exist within the literature. In-vitro performance can be evaluated by the evaluation of morphological changes of coatings after immersion in SBF. Qiu et al. reported the formation of clusters of fine precipitates for their HA-Ti porous coatings, with similar calcium mineralization efficiencies when using either crystalline HA or amorphous nanocrystalline HA [117]. In addition, these authors used the human osteosarcoma-derived SaOS-2 line with the aim to evaluate the cytotoxicity; cell viabilities after 48h proved that neither of the coatings was cytotoxic. On another hand, Gardon et al. [150] studied the differentiation and proliferation of cultured trabecular bone of Ti coatings onto PEEK obtaining a better biological response from Ti than PEEK from 3 days of culture, although optimal properties were shown with nanostructured titanium dioxide. Lee et al. [136] performed similar studies with cultured Human bone marrow mesenchymal stem cells hBMSCs (Human Bone Marrow Stromal Osteoprogenitor Cells) on HA-CS coated PEEK samples. The HA coating facilitated the differentiation and proliferation of cultured hBMSCs and promoted bone fusion with the surrounding iliac bone without the presence of any fibrous layer. Figure 9 illustrates some in-vivo results showing an association of the cylinders with the bone tissue improved as the recovery period in HA-coated PEEK disc group was increased. In contrast, the association of the cylinders with the bone tissue decreased for the animals implanted with the bare PEEK cylinder. Noorakma et al. [139] deposite an hydroxyapatite layer onto magnesium alloy substrate and demonstrates that In vitro behavior, superior cells adherence with numerous cellular micro extensions on porous Ta samples compared to Ti samples clearly suggests that Ta surfaces are biocompatible and cause no inhibition to bone cells (hFOB) adhesion and growth. Presence of relatively high ECM (Extra Cellular Matrix) mineralization on porous Ta samples also indicates that osteoblast cells have started differentiating and ECM remodeling [151]. In vivo, this porous tantalum biomaterial has desirable characteristics for bone ingrowth; further studies are warranted to ascertain its potential for clinical reconstructive orthopaedics [152].

The addition of graphene to HA coatings significantly enhanced attachment and proliferation of human osteoblast cells, which is most likely attributed to fast adsorption of key serum proteins like fibronectin with elongated stretching conformation on graphene [143].

5. Antibacterial/Antimicrobial coatings

Although the use of titanium and its alloys in biomedicine is still important, the infection around the implants remains as a concern. Infection not only do the patients suffer serious damage but bacterial infection after implant placement can cause significant complications thereby increasing medical cost. The paradigm of bacterial attachment and proliferation on surfaces was first recognized in the 1930s. It was established that a bacteria prefer to colonize a solid substrate than living in a planktonic state. The creation of antibacterial surfaces seeks to repel or resist the initial attachments of bacteria by either exhibiting an antibiofouling affect or by inactivating any cells coming into contact with the surface. Antibacterial surfaces can be divided in two groups: (i) antibiofouling surfaces that may resist or prevent cellular attachment due to the presence of an unfavorable surface topography or surface chemistry, and (ii) bactericidal surfaces that disrupt the cell on contact, causing cell death. The CS process has also emerged as a promising process to functionalize surfaces in such way.

The use of inorganic antimicrobial agents has attracted interest for its improved safety and stability verse organic antimicrobial agents. There has been a great development during recent years in antibacterial coatings but they are not still clinically much used; however, more developments and investigations are being explored to achieve both, excellent tissue integration ability and good antibacterial properties [153]. Silver (Ag) has already been highlighted as an antibacterial material. The combination of bioactivity (HA) and antibacterial properties (Ag) have been previously reported and the results indicated that the antibacterial activity increased with increasing HA-Ag nanopowder concentrations [144]. Alternatively, ceramic powder of zinc oxide (ZnO), calcium oxide (CaO) and magnesium oxide (MgO) have found antibacterial activity. Combinations of ZnO/Ti powders with different ratios have been performed to produce composite coated implants [154]; the results show that the viability of cells on ZnO20/Ti80 was higher than on ZnO50/Ti50 and ZnO80/Ti20 samples, thus proving that the cell viability decreased with increasing ZnO concentration in the coating composition. On the other hand, the bactericidal effect of TiO_2 coatings has also been extensively studied; specifically, CS anatase coatings were investigated by Kliemann et al. [123]. A kill rate of 99.99% was obtained after 5 min of expositng the bacteria Pseudomonas Aeruginosa to UV light with a peak intensity of 360 nm. Certain stagnation of the decay of the bacteria was foind, which could be attributed to non-coated areas present due to the impossibility of covering all the surface of the substrate by means of anchoring TiO_2 particles. Other coatings that are committed to antibacterial properties thank to ZnO are made of Novaron VZ 600 (a commercial available inorganic antimicrobial powder made from glass, with the functional material being ZnO) onto Ti [155]. Those studies were developed to analyze the differences among surfaces using different processing pressures and analysis of the antimicrobial with CS due to the low heat powder resistance. Results have shown that S.Areus cells on samples decreased after 24h culture, even on non-coated plates. Two possibilities were reported (i) Roughness can contribute to antimicrobial ability and (ii) medium concentration may have been too low for this bacterium.

Moreover, antibacterial coatings not only focus on orthopedic and implant applications, but also in touch surfaces where there is certain risk of infection. Metals like copper

(Cu) have been employed for this purpose. In the case of copper, its antibacterial activity not only comes from itself but also the utilized technique. The specific mechanism by which copper affects cellular structures is not yet proven, but the active agent of cell destruction is generally consider to be the copper ion [156]. As the fact that CS deals with high particle velocities leading to extreme work hardening and high dislocation density within the deposit, causes an increase of ion diffusion through the grain dislocations leading to microbial destruction [156]. Champagne et al. [156] produced copper surfaces onto aluminum using three thermal spray methods: plasma spray, wire spray and cold spray, in order to analyze the microbiologic differences and decrease the risk of infection of bacterial contamination on touch surfaces such a hospital table. CS produced the minimum percentage of MRSA (Meticikllin-Resistant Staphylococcus Aureus) due to the high number of dislocations within the coating.

Other attempts of antibacterial coatings were realized mixed with aluminum power (Al). The use of aluminum is cause for a number of cosmetic used, repair, corrosion and protection applications, also for its low density that could be accelerated to very high velocities in CS and the available commercially variety of composition of Al powders. Table 7 summarizes the CS spraying conditions used for the antibacterial coatings referenced within this section.

6. Summary

All the above coating systems try to satisfy the main requirements for a biocoating, either in biological (biocompatibility and bioactivity), mechanical or antibacterial terms. Terms like “structural design” and “deposition techniques” are involved in the development of the fabrication process to obtain cost-efficient products making it commercially reproducible and attainable to all types of markets. From this point of view, it is worth taking into consideration the valuable advantages that CS has to offer of non-microstructural changes from feedstock powder, high deposition efficiency, low temperature rates and overcoat the wide range of materials that could be applied. Day by day constant work and research demonstrate CS as a new technique to produce coatings.

However, still a big step has to be overcome in order to translate the experimental studies to the real market. More studies in vitro and in vivo from CS technique are required and the addition of antibacterial components must be performed as a necessity upturn in human health.

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Figure captions

Fig.1. Evolution of biomaterials science and technology

Fig.2. Bioactivity spectrum for various bioceramic implants: (a) relative rate of bioactivity and (b) time dependence of formation of bone bonding at an implant interface [(A) 45S5 Bioglass®, (B) Mina13 Ceravital®, (C) 55S4.3 Bioglass®, (D) A/W glass-ceramic, (E)HA, (F) KGy213 Ceravital®] [6]

Fig.3. Variables and stages of coating formation in conventional thermal spray processes

Fig.4 Schema of TS techniques according to energy source

Fig.5. Schema of CS technique

Fig.6. Stages of coating formation in the cold spray process [97]

Fig.7. Porous Ti coatings by CS from less to high energetic conditions (a-d) [122]

Fig.8. Porous Ti coatings (a) SEM free surface image and (b) MO Cross section image [126], (c) SEM free surface image (d) SEM cross section image[127]

Fig.9. In vivo evaluation of bare PEEK and HA-PEEK at 4 weeks (a) and 8 weeks (b) [141]

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Figure
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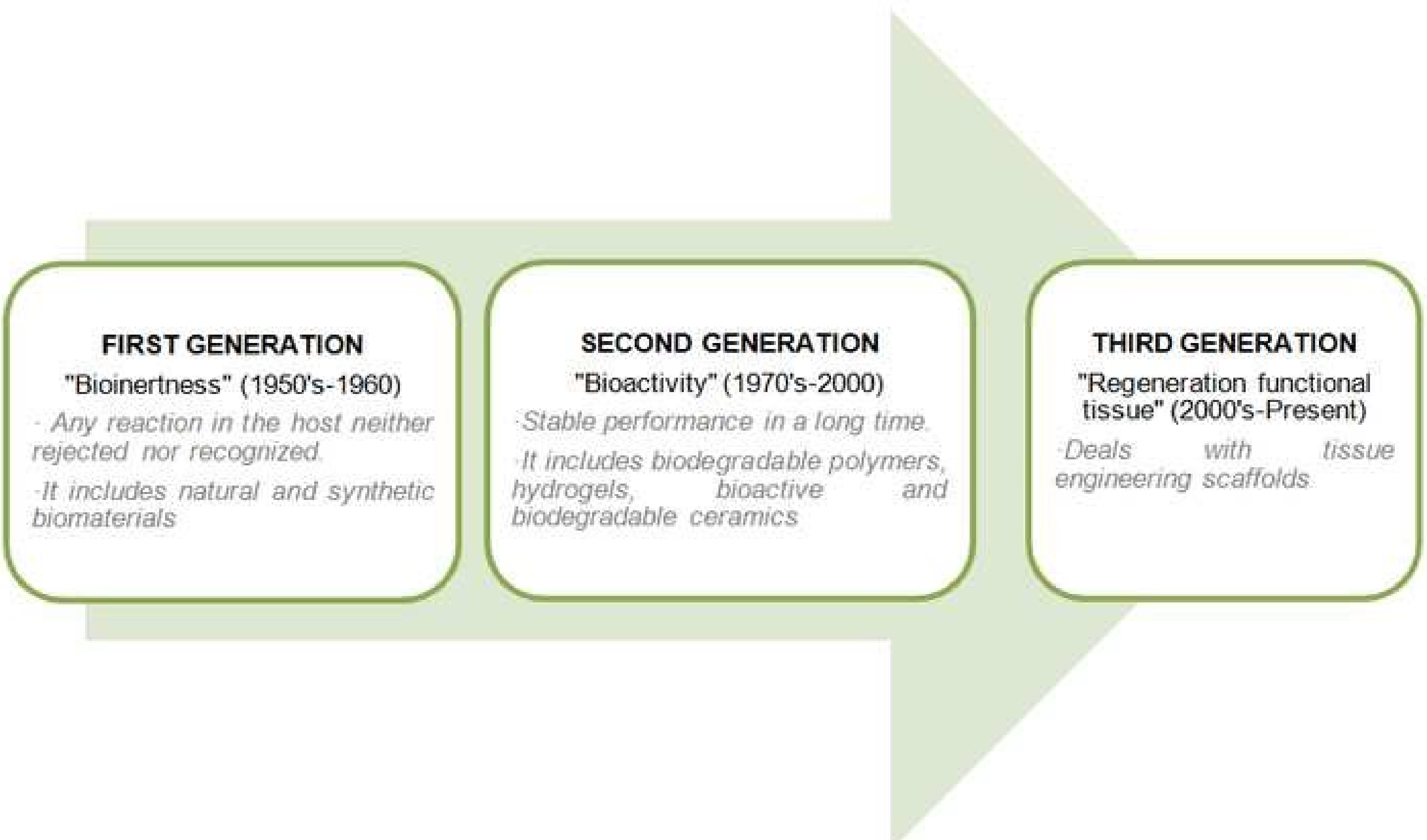

Figure
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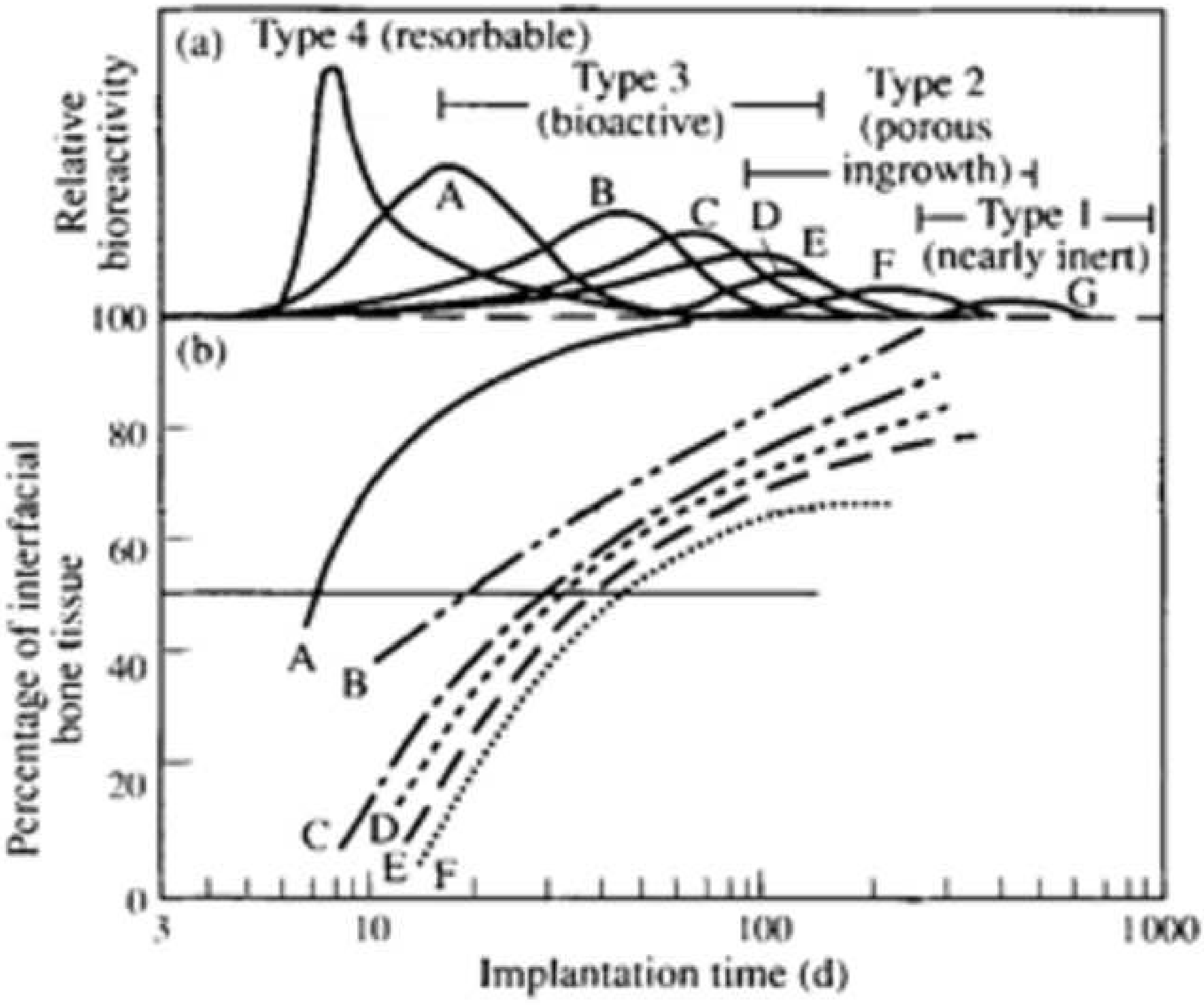

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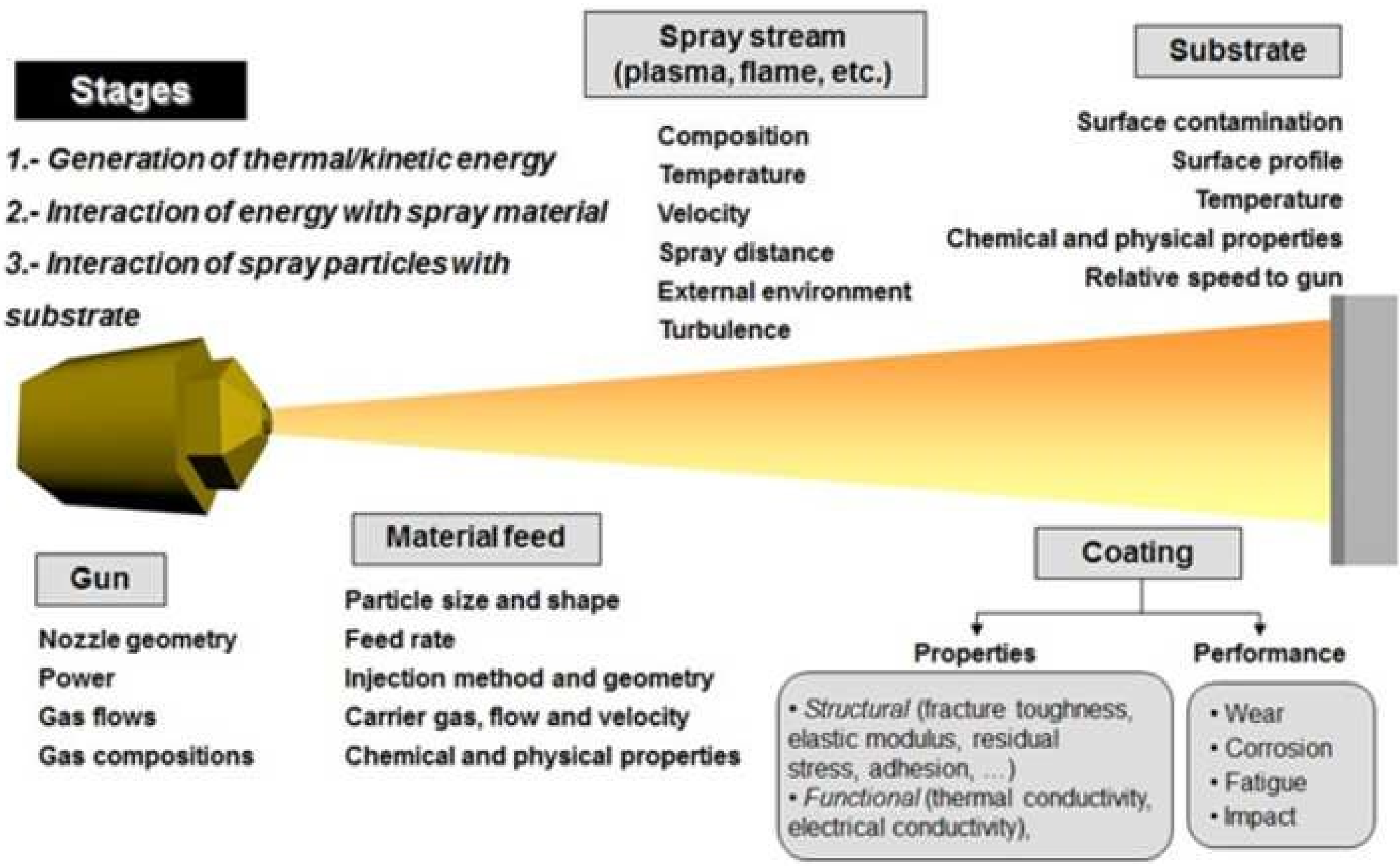

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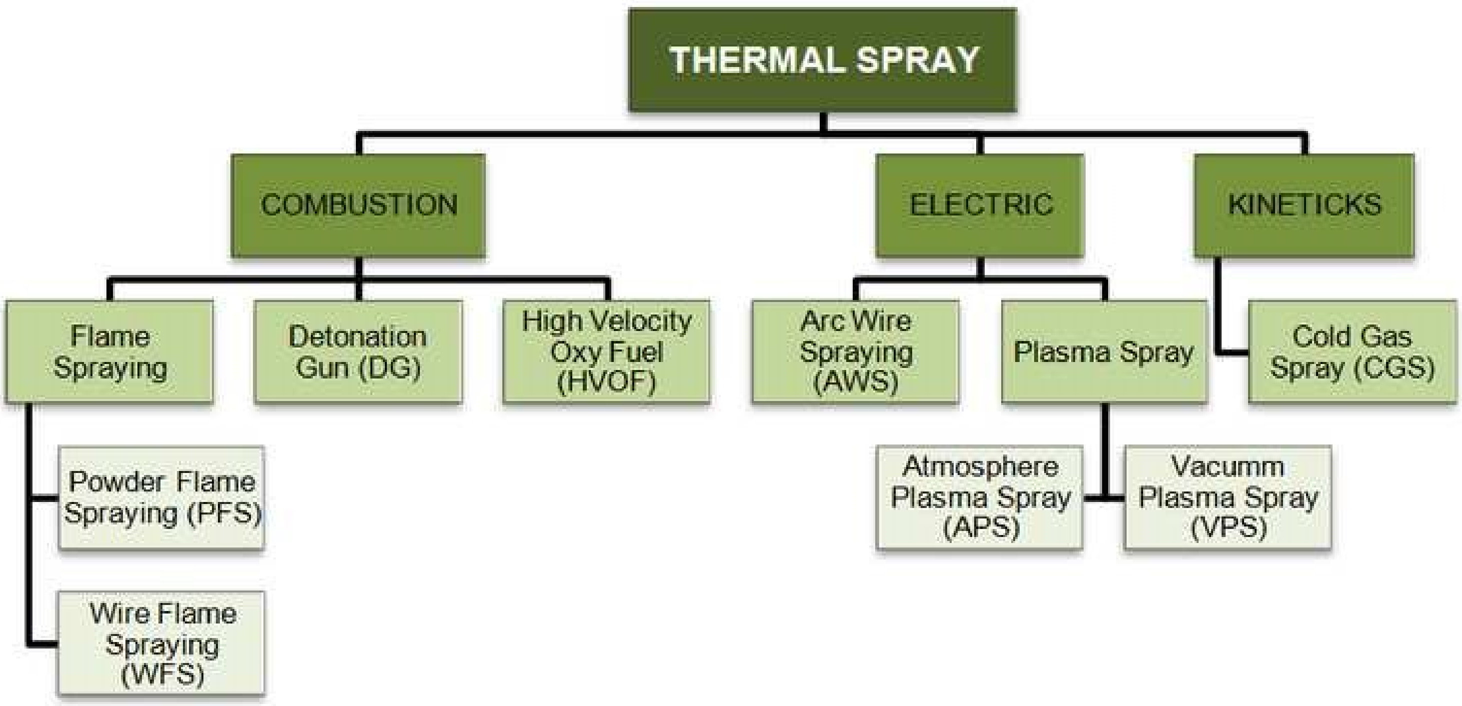

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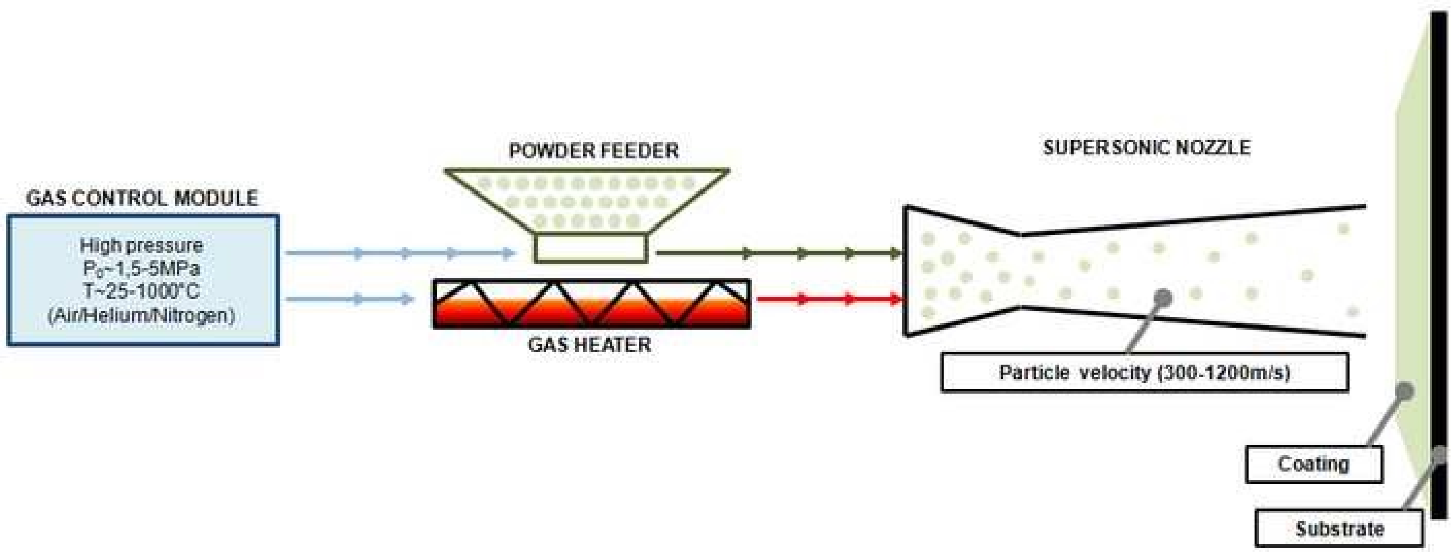

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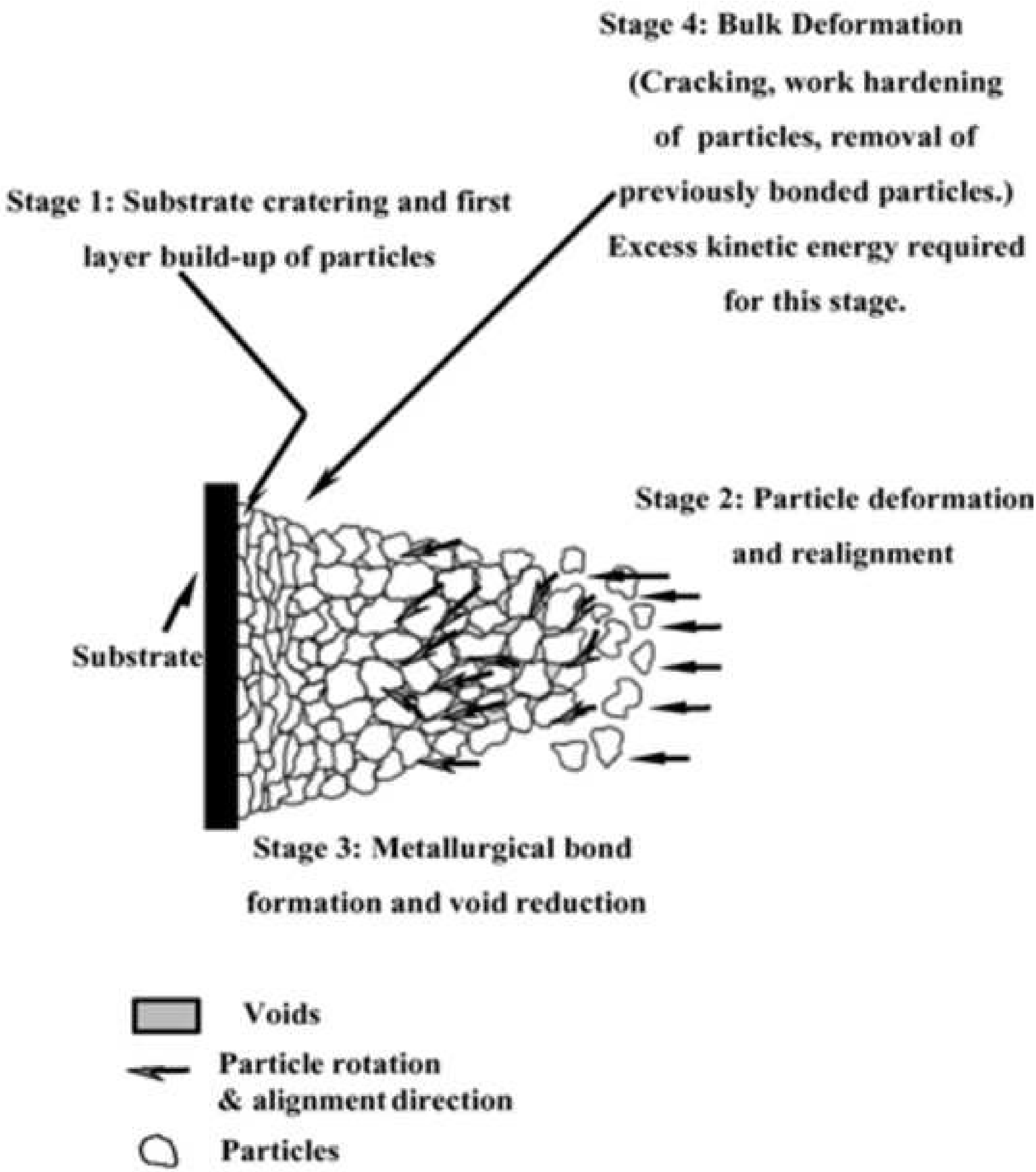

Figure
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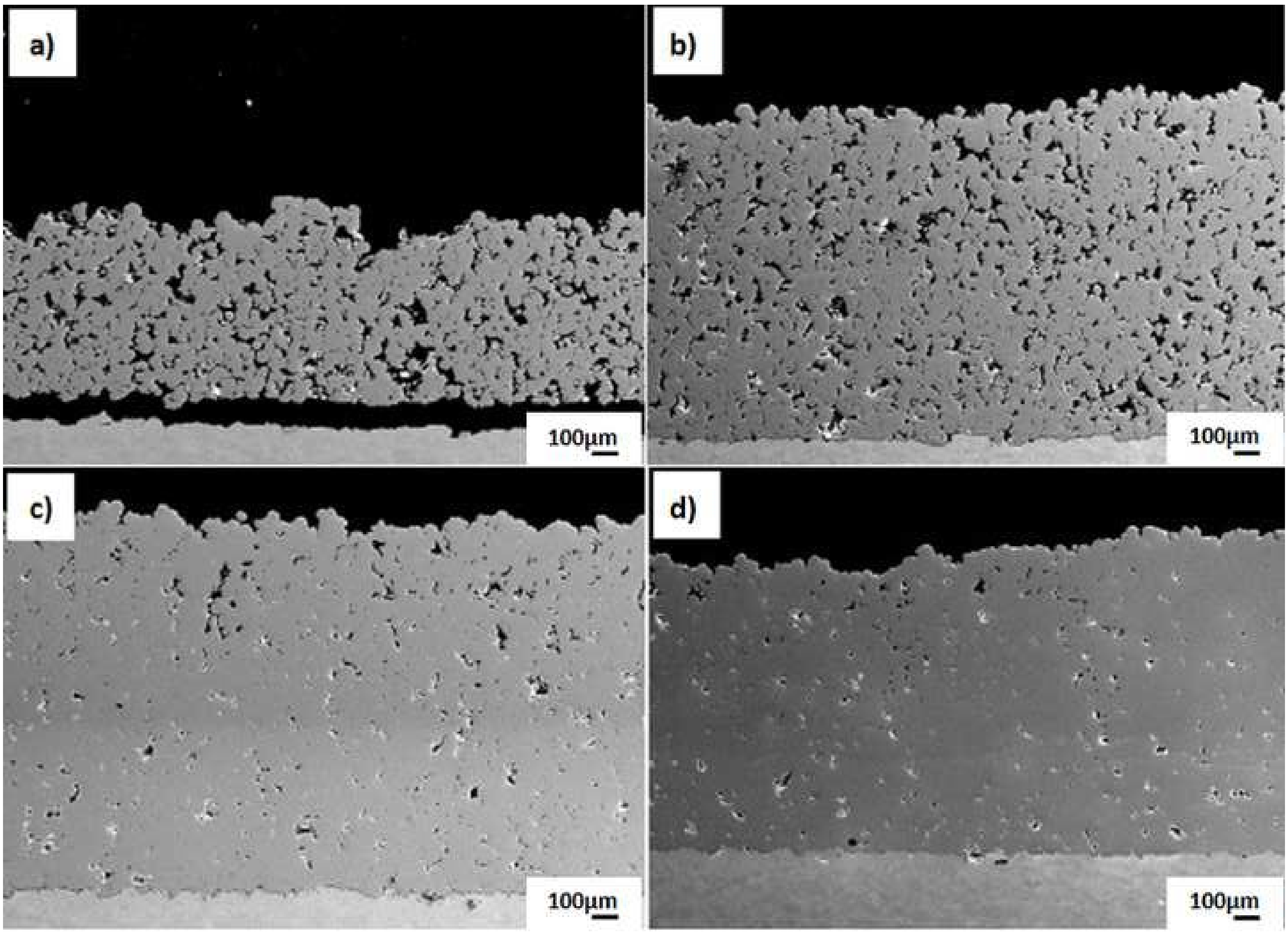

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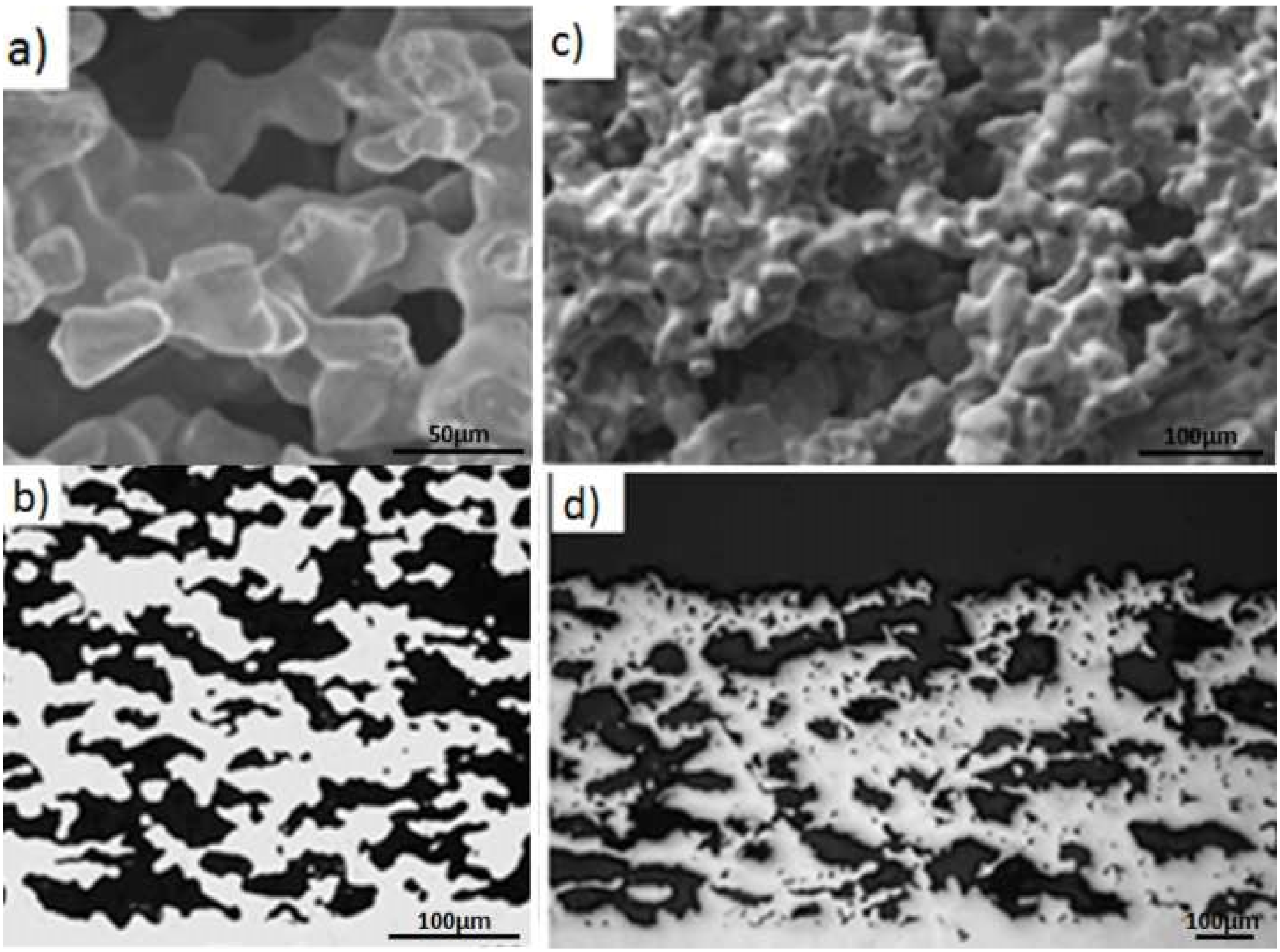

Figure

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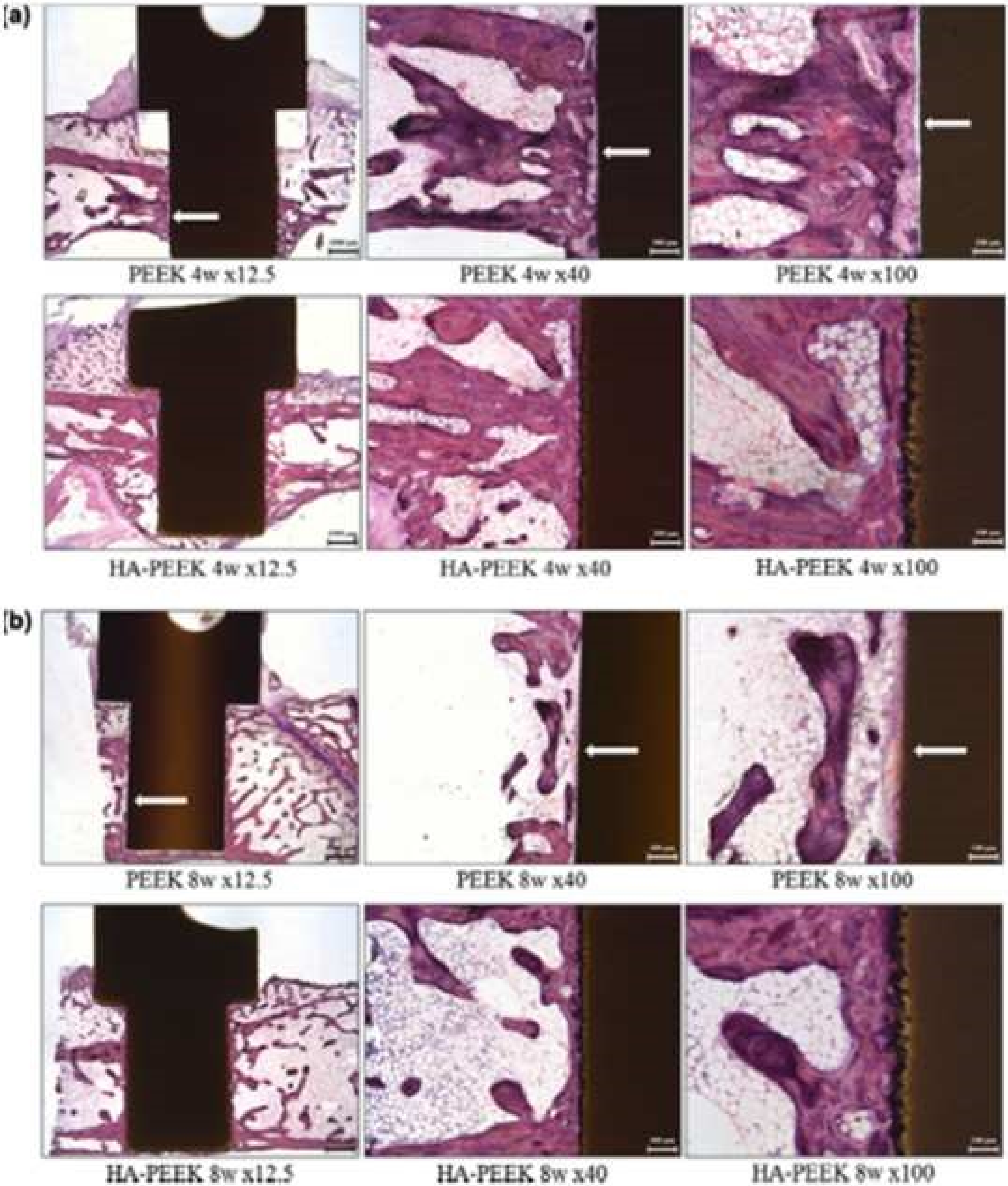

Table 1

Requirements of HA coatings for implants for surgery [61-65]

Property	Specification
Ca/P ratio	1.67-1.76
Hydroxyapatite phase	≥50%
Limits of specific trace elements	50 mg/kg
Hydroxyapatite phase	>50%
TCP, TTCP, CaO phases	≤5% mass fraction
Crystallinity	≥45 % of the 100 % crystalline hydroxyapatite
Tensile Strength	≥15MPa
Shear Strength	≥22 MPa

Table 2

Advantages and inconvenients of TS to other technologies for HA spraying [66-69]

Technique	Advantages	Inconvenients
Thermal spraying	-High deposition rates -Low cost	-Line of sight technique -High temperature induce decomposition -Rapid cooling produces amorphous coatings -Lack of uniformity -Crack appearance -Low porosity -Coating spalling and interface separation between the coating and the substrate
Sputter coating	-Uniform Coating thickness on flat substrates -Dense coating -Homogenous coating -High adhesion	-Line of sight technique -Expensive time consuming -Produces amorphous coatings -Low crystallite which accelerates the dissolution of the film in the body
Pulsed laser deposition	-Coating with crystalline and amorphous faces - Dense and porous coating -Ability to produce wide range of multilayer coating from different materials -Ability to produce high crystalline HA coating -Ability to restore complex stoichiometry -High degree of control on deposition parameters	-Line of sight technique -Splashing or particle deposition -Need surface pretreatment -Lack of uniformity
Dip coating	-Low cost -Quick technique -Produce complex coat substrates -High surface uniformity -Good speed of coating	-Requires high sintering temperatures -Thermal expansion mismatch -Crack appearance
Sol-Gel	-Can coat complex shapes -Low processing temperatures -Relatively cheap as coatings are very thin -Simple deposition method -High purity -High corrosion resistant -Fairly good adhesion	-Some processes require controlled atmosphere processing -Expensive raw materials -Not suitable for industrial scale -High permeability -Low wear resistance -Hard to control the porosity
Electrophoretic deposition	-Uniform coating thickness -Rapid deposition rates -Can coat complex substrates -Simple setup -Low cost -High degree of control on coating morphology -and thickness -Good mechanical strength -High adhesion for n-HA	-Difficult to produce crack-free coatings -Requires high sintering temperatures -HA decomposition during sintering stage -Substrate must have electrical conductivity
Hot isostatic pressing	-Produce dense coatings -Produce net-shape ceramics -Good temperature control -Homogeneous structure -High uniformity -High precision -No dimensional or shape limitation	-Cannot coat complex substrates -High temperature required -Thermal expansion mismatch -Elastic property differences -Expensive -Removal/interaction of encapsulation material
Ion beam assisted deposition	-Low temperature process -High reproducibility and reliability -High adhesion -Wide atomic intermix zone are coating-to-substrate interface	-Crack appearance on the coated surface
Dynamic mixing method	-High adhesive strength	-Line of sight technique -Expensive -Produces amorphous coatings
Biomimetic coating	-Low processing temperatures -Can form bonelike apatite -Can coat complex shapes -Can incorporate gone growth stimulating factors	-Time consuming -Requires replenishment and a constant of pH of simulated body fluid
Solution deposition	-A low-temperature precipitation process resulting in a pure, highly crystalline, firmly adherent HA coating. Good for coating evenly for porous and beaded surfaces.	-Maximum thickness of 20 microns limits its use as a primary mode of fixation
Electrochemical deposition (ECD)	-Uniform coating -Simply set up	Low tear strength Poor adherence

	-Control morphologies coating -Low temperatures -Coat highly irregular objects	
Atomic layer deposition	-Suitable for preparation nanoscale HA and coating three-dimensional structures where exact film conformality is needed	Poor crystallinity
PVD	-Thin layers -More adherent to the underlying titanium surface than thermal spray less prone to crack formation	Expensive technique
CVD	-Ability to modulate precursor concentrations during deposition to create functionally graded coatings	Expensive technique

Table 3

The human impact and the size of the commercial market for biomaterials and medical devices [3]

Application	Biomaterials used	Number/year – World (or World Market in US$)
Joint replacements (hip, knee, shoulder)	Titanium, stainless steel, polyethylene	2.500.000
Bone fixation plates and screws	Metals, poly(lactic acid) (PLA)	1.500.000
Spine disks and fusion hardware	-	800.000
Bone cement	Poly(menthyl methacrylate)	($600M)
Bone defect repair	Calcium phosphates	-
Artificial tendon or ligament	Polyester fibers	-
Dental implant-tooth fixation	Titanium	($4B)
The biomaterials and healthcare market: Facts and figures (per year)		
Total US healthcare expenditures (1990)		$714 billion
Total US healthcare expenditures (2009)		$2.5 trillion
Total US health research and development expenditure (2009)		$139billion
Number of medical device companies in the US		12.000
Jobs in the US medical device industry (2008)		425.000
Sales by US medical device industry (2008)		$136 billion
World medical device market forecast for 2013		$286 billion

Table 4

Surface description of some of the commercial orthopedic implants [92]

Manufacturer	Surface description
Biomet	-Regenerex™: porous Ti alloys -RoughCoat™: sintered Co-Cr bead porous coating with and without plasma-sprayed HA
DePuy	-Oription™: porous coating, porous pure Ti alloy coating -Purocoat®: porous coating, sintered Co-Cr beads -Duofix® HA: plasma sprayed HA over Purocoat® coating
Smith & Nephew	-Stikite: porous three-dimensional asymmetric Ti powder coating -RoughCoat™: sintered Co-Cr bead porous coating with and without plasma-sprayed HA
Stryker	-PureFix™ HA: plasma-sprayed HA -Peri-Apatite™: solution deposited HA coating that uniformly coats three-dimensional porous ingrowth surfaces -Plasma sprayed cpTi with and without PureFix™ HA coating -Arc-deposited cpTi with PureFix™ HA coating
Zimmer	-Trabecular Metal™: open cell porous tantalum construct -CSTi™, Cancellous-Structured Titanium™ coating with and without plasma-sprayed HA coating -Fiber metal: Ti fiber with and without plasma-sprayed HA/TCP coating -CoCr-beaded ingrowth surfaces
Arcam AB	-Trabecular Structures ™ : titanium deposition via Electron Beam Melting (EBM)
Astra Tech AB	OsseoSpeed™: grit blasting titania (TiO_2), followed by hydrofluoric acid (HF) treatment
BIOMET 3i Implant Innovations	Nanotite™: CaP nanoparticle features

Table 5

CS conditions of metals coatings for biomedical applications

	Feedstock powder	Substrate	Gas	Gas temperature [°C]	Gas pressure [bars]	Standoff distance [mm]	Traverse Speed [mm/s]
Li et al.[113]	Ti Ti6Al4V	Ti6Al4V	Air	520	28	30	-
Sun et al.[116]	Ti+Mg	Titanium	He	340	10	-	-
Qiu al.[117]	CpTi+CpAl CpTi+CpAl+HA	Ti	He	370	6.9	12.5	1.66
Al-Mangour et al.[120]	SS 316 + L605alloy	Mild Steel	N_2	700	40	80	300

Table 6

CS conditions of HA/Ti and HA coatings for biomedical applications

	Feedstock powder	Substrate	Gas	Gas temperature [°C]	Gas pressure [bars]	Standoff distance [mm]	Traverse Speed [mm/s]
Qiu al.[117]	Cp Ti+Cp Al Cp Ti+Cp Al+HA	Ti	He	370	6.9	12.5	1.66
Noorakma et al. [139]	HA	AZ51 alloy	*Air*	500-700	10	40	-
Lee et al. [141]	HA	PEEK	Air	200/300/ 400	7/14/20	30	-
Zhou et al.[146]	Cp Ti+HA	Ti	N_2	700	35	15	-
Choudhurin et al. [147]	Cp Ti Sponge Ti Sponge Ti+HA	Ti	N_2	400-700	25-38	25	50-400

Table 7

CS conditions of antibacterial coating

	Feedstock powder	Substrate	Gas	Gas temperature [°C]	Gas pressure [bars]	Standoff distance [mm]	Traverse Speed [mm/s]
Sanpo et all. [149]	HA-Ag (Ag-doped HA) +PEEK	Glass	Air	150-160	11-12	15	50
Sanpo et all. [154]	ZnO+Ti	Al 6061	He	300-400	13-15	15	60
Tami et all.[155]	Novaron VZ 600	Ti	N	350	30	5	20