

CoCrMo alloy as biomaterial for bone reconstruction in oral and maxillofacial surgery: A scoping review.

Aleación de CoCrMo como biomaterial para la reconstrucción ósea en cirugía oral y maxilofacial: una revisión del alcance.

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Abstract: Background: Osseointegration allowed for a breakthrough in biomaterials and techniques and it has contributed to increased application of dental implants. However, insufficient bone level is a frequent problem and it creates an anatomically less favourable base for implant placement. The first surgical procedure should comprise the reconstruction of the alveolar bone height. CoCrMo alloys are nowadays considered as highly corrosion resistant and biocompatible materials in dentistry, and therefore has been suggested as a suitable biomaterial for guided bone regeneration and tissue engineering. **Aim:** To determine the use of CoCrMo alloy for implantable devices in oral and maxillofacial surgery and to discuss the potential of this alloy for bone regeneration and repair through a scoping review. **Material and methods:** The search was done by using various databases including PubMed, Thomson Reuters and Scopus. We selected English literature related to studies reporting the CoCrMo properties and manufacturing processes and findings related to bone-forming techniques. Data was compared qualitatively. **Results:** 90 studies were selected according to the inclusion criteria. We reported different manufacturing techniques and their advantages related to mechanical, chemical and biocompatible properties. **Conclusion:** Improved tissue reactions of CoCrMo implant devices can be acquired by the application of novel techniques and surface modifications. Moreover, several processes have demonstrated to improve the *in vitro* and *in vivo* biocompatibility of the CoCrMo alloy to promote the attachment, proliferation and guided differentiation of seeding cells.

Keywords: Bone regeneration; alveolar ridge augmentation; CoCrMo alloy; dental implants; biocompatible materials.

Resumen: Antecedentes: La osteointegración ha permitido un gran avance en biomateriales y técnicas, y ha contribuido un mayor uso de implantes dentales. Sin embargo, la existencia de un nivel óseo insuficiente es un problema frecuente y crea una base anatómicamente menos favorable para la colocación de implantes. El primer procedimiento quirúrgico debe comprender la reconstrucción de la altura del hueso alveolar. Las aleaciones de CoCrMo se consideran hoy en día como materiales altamente resistentes a la corrosión y biocompatibles en odontología y, por lo tanto, se ha sugerido como un biomaterial adecuado para la regeneración ósea guiada y la ingeniería de tejidos. **Objetivo:** Determinar el uso de la aleación CoCrMo para dispositivos implantables en cirugía oral y

maxilofacial y discutir sobre el potencial de esta aleación para la regeneración y reparación ósea a través de una revisión de alcance. **Material y Métodos:** La búsqueda se realizó utilizando varias bases de datos, incluidas PubMed, Thomson Reuters y Scopus. Se seleccionó literatura inglesa relacionada con estudios que informan sobre las propiedades de CoCrMo y los procesos de fabricación y los hallazgos relacionados con las técnicas de formación de huesos. Los datos se compararon cualitativamente. **Resultados:** Se seleccionaron 90 estudios según los criterios de inclusión, y se reportaron diferentes técnicas de fabricación y sus ventajas relacionadas con propiedades mecánicas, químicas

y biocompatibles. **Conclusión:** Las reacciones tisulares mejoradas de los dispositivos de implante CoCrMo pueden adquirirse mediante la aplicación de nuevas técnicas y modificaciones de la superficie. Además, varios procesos han demostrado mejorar la biocompatibilidad *in vitro* e *in vivo* de la aleación CoCrMo para promover la unión, proliferación y diferenciación guiada de las células de siembra.

Palabra Clave: Regeneración ósea; aumento de la cresta alveolar; aleación de CoCrMo; implantes dentales; materiales biocompatibles

INTRODUCTION.

Lack of alveolar bone is one of the most prevalent and difficult problems to address in implant surgery. The first surgical procedure should comprise the reconstruction of the alveolar bone height, and oral surgeons have to decide whether the use of previous or simultaneous regenerative process is appropriate for each patient, in order to provide a restoration with a good long-term prognosis. Many methods have been developed and employed over the time. In the past, autogenous onlay bone grafts, xenografts and various bone substitutes were used for the improvement of horizontally and vertically shrunken alveolar ridges.¹ However, these techniques had some drawbacks such as the need of additional surgery or presence of pain, seroma, bleeding, and infection in the donor site, immune responses, potential transfer of infectious agents and technical difficulties with vascularised grafts, among others.

The limited success of auto- and allografts in some clinical situations has stimulated the investigation of a wide variety of biomaterials to be used for the induction and support of alveolar bone growth.^{2,3} The bulk composition of biomaterials and their surface plays an extremely important role in the response of artificial medical devices to the biological environment. The efficacy of these implants is determined by their properties and it is highly influenced by surface characteristics such as morphology, microstructure and composition.

Titanium is recognized as the gold standard material in oral implantology due to its well-known properties of biocompatibility, low density, high resistance, high

rigidity, excellent osseointegration and biological stability.⁴ However, when it comes to biomaterials for bone regeneration, CoCrMo alloy is an alternative as it is highly resistant to corrosion and due to its biocompatibility, and as such it has been suggested as a suitable biomaterial for guided bone regeneration (GBR) and tissue engineering.⁵⁻⁷

Although it is known to be less biocompatible than titanium and its alloys, it has many superior mechanical properties (e.g. stiffness and toughness). Cobalt-based alloys were extensively used in cast and hard facing forms and a wide range of studies that focus in new manufacturing processes and surface coatings can be found.⁸⁻¹⁰ Because of their resistance to corrosion and wear, biocompatibility and excellent strength and toughness at high temperature,¹¹ typical applications of the Co-based alloys include the manufacturing of customized abutments, crowns and bridges for oral implantology, orthodontic dental archwires, and screw-retained restorations, and as plates and membranes for bone regeneration in the maxilla.¹²⁻¹⁴

Mechanical properties and their relationship with implant microstructure and with the structural and material properties of bone are defined in terms of static and dynamic charges applied during function within the host environment. Chemical properties focus on corrosion behaviour, the nature of the passive films and the closely related ion release.¹⁵

Surface energy and surface charges are relevant for understanding the biological response when a material is implanted in the body. The main limitation of metallic biomaterials such as the CoCrMo alloy is the release

of toxic metallic elements, produced by corrosion that can lead to a variety of adverse tissue reactions and/or hypersensitivity reactions.^{16,17}

Therefore, the research is focused on the improvement of actual materials starting from their manufacturing process and/or coatings, and their combination with other components, such as growth factors (GF), platelet-rich plasma (PRP) and bone morphogenetic proteins (BMPs), which promise alternatives for bone repair, or new techniques for the treatment of classical bone diseases.¹⁸

This article provides a brief overview of the composition, manufacturing and use of CoCrMo alloy while focusing on its potential for bone regeneration and repair in the field of oral and maxillofacial surgery. The aim of this study is to determine the use of CoCrMo alloy for implantable devices in oral and maxillofacial surgery and to discuss the potential of this alloy for bone regeneration and repair.

MATERIALS AND METHODS.

Study design

This study was performed in compliance with the PRISMA guidelines.¹⁹

Eligibility criteria

Studies were eligible for inclusion if they broadly described the manufacturing techniques of CoCrMo implant devices and *in vitro* and *in vivo* studies of CoCrMo alloys to identify and characterize the existing literature or evidence. We selected literature in English related to studies published from 2014 to the present, reporting

the CoCrMo properties, and manufacturing processes and findings related to bone augmentation techniques. In addition, we included previous literature with respect to bulk composition and basic knowledge of the alloy.

Reviews, case reports, case series and expert opinions were excluded from the analysis, but their reference lists were reviewed to identify additional articles.

Literature search and study selection

The search was carried out by two researchers through reading, synthesis of information collected and selection of articles that met the eligibility criteria. The literature search was performed using *PubMed*, *Thomson Reuters* and *Scopus* databases and it was divided in three separated areas:

- Articles concerning to CoCrMo composition and manufacturing (keywords: *CoCrMo microstructure*, *CoCrMo alloys for biomedical application*, *CoCrMo manufacturing*);
- CoCrMo properties (keywords: *CoCrMo surface properties*, *CoCrMo mechanical properties* and *CoCrMo chemical properties*);
- Use of CoCrMo alloy for bone regeneration (keywords: *CoCrMo biocompatibility*, *CoCrMo+bone*).

Data analysis

Included studies were evaluated in a qualitative manner and no statistical analyses were performed. Assessed outcomes were improved properties of CoCrMo from different manufacturing methods or the addition of elements and coatings; differences between bulk CoCrMo alloy and improved implant surfaces; and bone regeneration or new bone formation.

Figure 1. Flow diagram of the selection process of records used in this review, according to the PRISMA guidelines.¹⁹

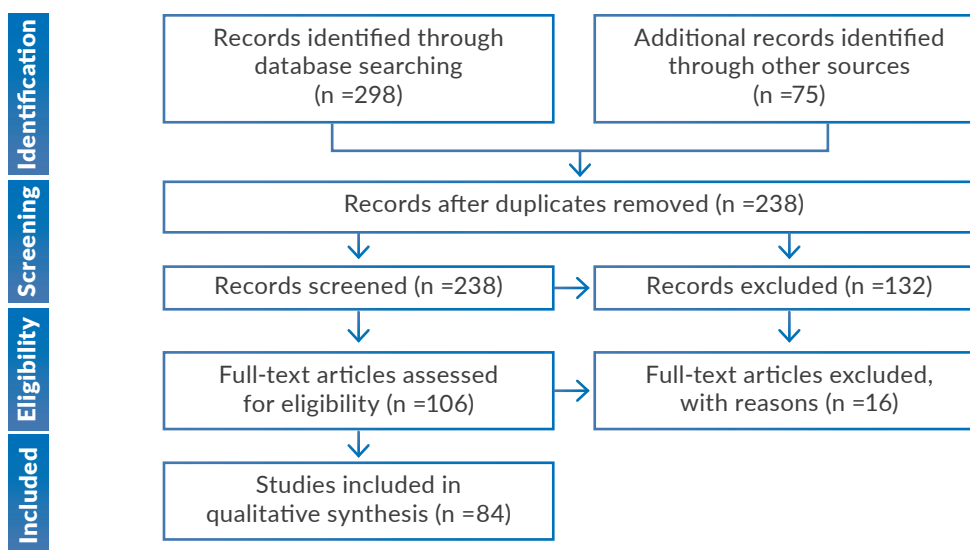


Figure 2. A) Co-Cr binary phase diagram of the Co-Cr system.²⁹

B) Effects of alloying elements on the temperature of the transformation from HCP Co to FCC Co as a function of solubility of the elements in FCC Co. SFE (stacking Fault Energies). Adapted from 28.²⁸

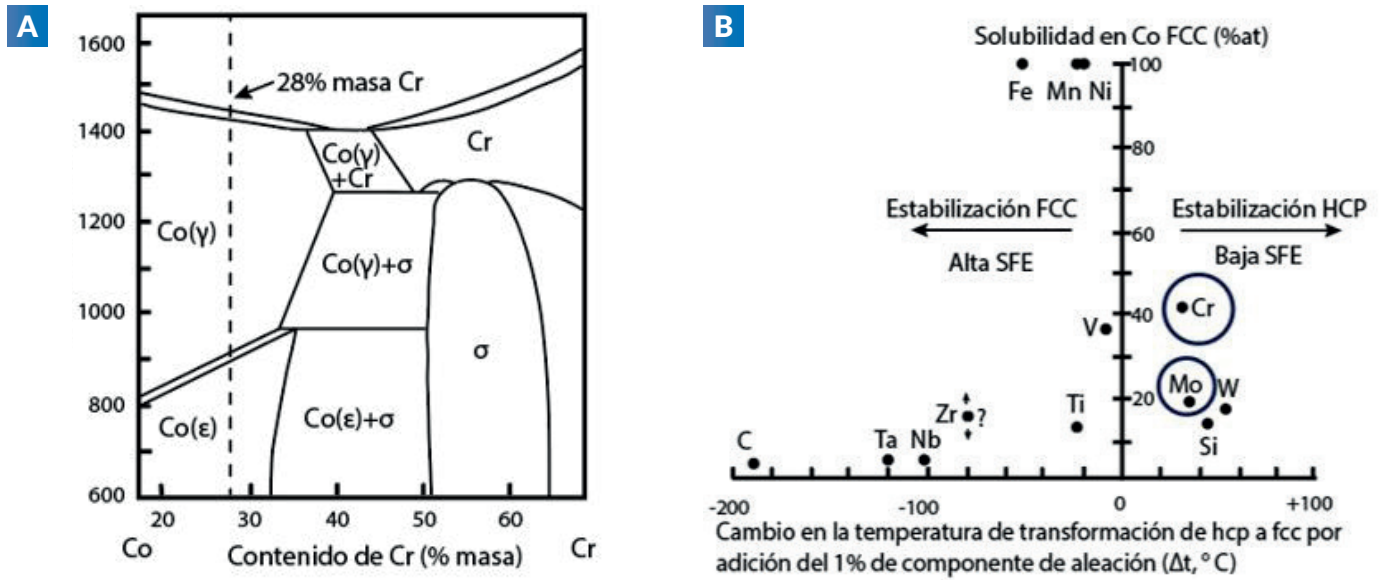


Figure 3. A) $M_{23}C_6$ type (blocky dense). B) $M_{23}C_6$ type (starlike with stripe patterns).

C) M_7C_3 type (starlike with complicated microstructures). Adapted from.³²

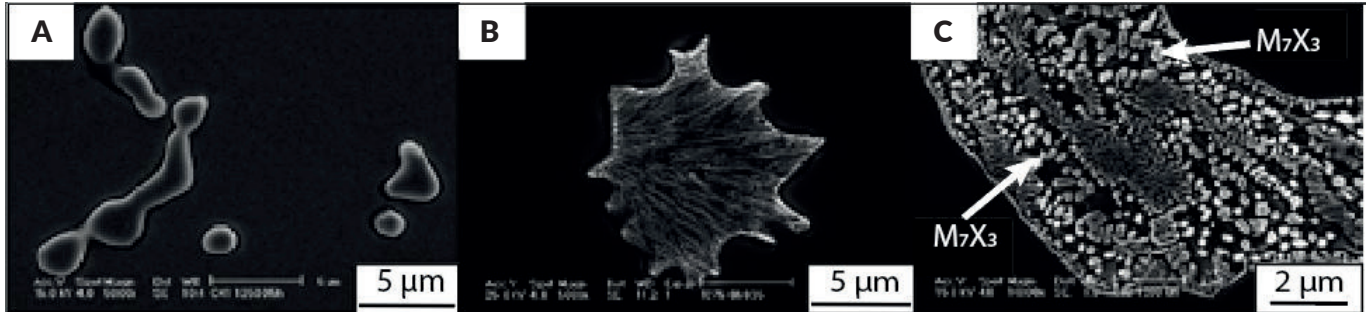


Figure 3. Schematic representation of a crevice corrosion attack on the surface of CoCrMo alloy. Adapted from .³¹

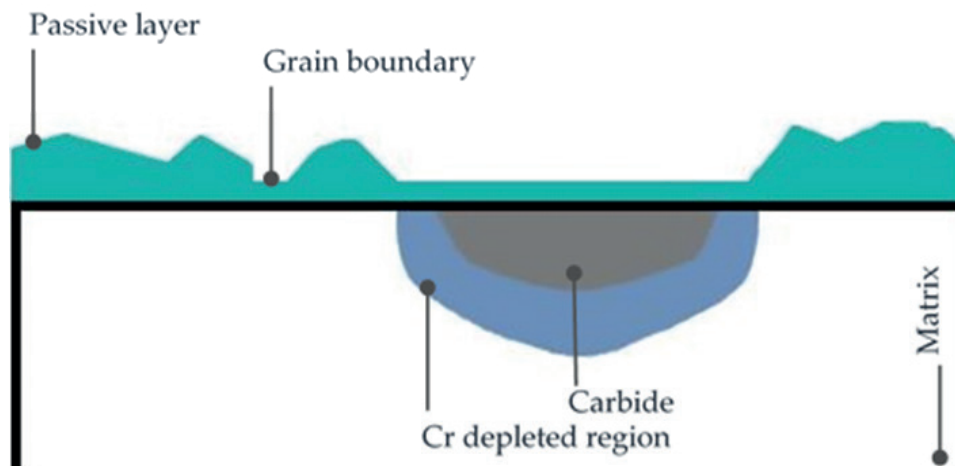


Table 1. Chemical composition of the standard ASTM F75.²⁰

Element	Composition [%] (Mass/Mass)	
	minimun	maximun
Chromium	27.00	30.00
Molybdenum	5.00	7.00
Nickel	-	0.50
Iron	-	0.75
Carbon	-	0.35
Silicon	-	1.00
Manganese	-	1.00
Tungsten	-	0.20
Phosphorous	-	0.020
Sulphur	-	0.010
Nitrogen	-	0.25
Aluminium	-	0.10
Titanium	-	0.10
Boron	-	0.010
Cobalt	balance	balance

Table 2. Mechanical requirements of ASTM F7520.²⁰

Property		
Young's modulus	3×10 ⁷ (210)	[psi (GPa)]
Ultimate tensile strength	95000 - 130389 (655-899)	[psi (MPa)]
Yield strength (0.2% offset)	64977 - 74985 (448-517)	[psi (MPa)]
Fatigue strength	30023 - 44962 (207-310)	[psi (MPa)]
Elongation (min)		8 [%]
Reduction of area (min)		8 [%]

Table 3. Surface modification methods to improve the biocompatibility of CoCrMo from *in vitro* studies.

Surface modification	Culture Medium	Conclusion	Ref
Graphene coating	Mice BMSCs in Dulbecco's Modified Eagle's Medium	Graphene coating enhanced the adhesion and proliferation of bone marrow mesenchymal stem cells. A graphene coating for surface modification of CoCrMo alloy provides a viable option for <i>in vivo</i> application of graphene materials and improves the biocompatibility of CoCrMo alloy.	76
SLM 3D-printed Co-Cr-Mo	L929 mouse fibroblast cells in Dulbecco's modified eagle medium	All the SLM samples with different roughness supported the attachment and proliferation of L929 fibroblast cells during our experiments and were comparable to the as-cast reference (which was more homogeneous and had the smoothest surface roughness). There may be complexities associated with SLM implants and the cell attachment or bone ingrowth, for example, may be affected throughout a single Co-Cr-Mo device due to part orientation in build chamber because this is more influenced by the amplitude than by the morphology of the surface	78

Surface modification	Culture Medium	Conclusion	Ref
Milling/post-sintering (MPS)	L929 mouse fibroblasts in RPMI 1640 culture medium	The MPS specimens showed smaller releases of Co ions than the cast control group. Cell morphology was normal in both groups; cell viability was higher in the MPS than in the cast. The MPS-fabricated Co–Cr alloy showed better <i>in vitro</i> biocompatibility than the cast one.	79
Hidroxyapatite-TiN coating	SBF	Layer of HA with low intensity managed to form on the surface of the TiN coated CoCrMo alloys.	80
TiO ₂ coating	Human MSCs in complete growth medium, α -minimum essential medium	Osteogenic differentiation was shown to be enhanced on CoCrMo-TiO ₂ compared to CoCrMo, with increased calcium ion content per cell, greater hydroxyapatite nodule formation and reduced type I collagen deposition per cell. The expression of the focal adhesion of vinculin was shown to be slightly greater. CoCrMo-TiO ₂ requires more strength to remove a single cell from the substrate surface compared to CoCrMo, suggesting that TiO ₂ coatings may have the potential to increase the biocompatibility of CoCrMo implantable devices.	59
TiO ₂ coating	SBF	Better hydroxyapatite deposition characteristic has been observed after SBF tests on the oxidised sample as compared to the conventional CoCrMo alloy.	60
Graphene coating	Mice bone marrow mesenchymal stem cells (BMSCs) in Dulbecco's Modified Eagle's Medium	Enhanced cell adhesion and cell proliferation of BMSCs	77
Diamond-like coating (DLC)	Osteoblasts from mouse calvaria cultured in α -minimum essential medium	Enhanced biocompatibility of DLC films compared with that of CoCrMo. DLC tending to diamond structure (sp ³ content) exhibited better biocompatibility compared with that tending to graphite structure (sp ²) because of the absence of repulsive forces.	81
Niobium (Nb)-reinforced hydroxyapatite (HA) coating	MG-63 cells (osteoblast-like adherent cells) cultured in Gibco RPMI 1640 media	Increased cell proliferation as compared to the uncoated CoCr alloy	82
Sand blasting with Al ₂ O ₃ + acid etching: 50 μ m Al ₂ O ₃ (SLA50) or 250 μ m Al ₂ O ₃ (SLA250)	Human MSCs in α -minimum essential medium	SLA250 surface promoted a superior level of bioactivity by enhancing cell adhesion, proliferation, and markers of osteogenic differentiation, despite the presence of low levels of aluminium residue	83

RESULTS AND DISCUSSION.

Search process

Study design is illustrated in Figure 1. Initial search resulted in 373 studies, which was reduced to 238 after limiting the results to the inclusion criteria. A total of 238 articles were screened by reviewing titles and abstracts, yielding 106 studies.

Finally, 90 studies were included after meticulous assessment of the full-texts based on inclusion and exclusion criteria. Thirteen referred to CoCrMo composition and manufacturing,³⁴ to CoCrMo properties and 43 to CoCrMo alloy for bone regeneration.

Composition, manufacturing and microstructural characterization

Although there are several specifications for Co-based alloys, the main alloys used are Co-28Cr-6Mo cast alloys according to the ASTM F75 standard,²⁰ Co-20Cr-15W-10Ni wrought alloy (ASTM F90) and Co-35Ni-20Cr-10Mo (ASTM F562).²¹ Two types of Co-based alloys are extensively used in implant fabrications. The first type is the castable CoCrMo alloy known as Vitallium (Howmedica, Inc.) that was formerly introduced in 1936 by Venable and Stucke²² and is still in use.

Other current commercial names of F75 alloy are Haynes Stellite 21 (Cabot Corp.), Protasul-2 (Sulzer AG), and Zimaloy (Zimmer). The second group of alloys is processed by hot forging (wrought alloys) and contains tungsten and a higher nickel content. The two basic elements of the CoCr alloys form a solid solution of up to 65% Co and the rest are important residual elements (Table 1).

The as-cast CoCrMo alloy is widely used in the manufacturing of implantable devices made with investment casting techniques. Because of these alloys' hard workability and the shape complexity of the prostheses and implantable devices, this process reduces the high cost of machining operations by producing pieces whose dimensions are close to the final ones. The cast alloys contain up to 0.35% carbon to improve the castability by lowering the melting temperature to approximately 1350°C.

The normal fabrication involves a lost-wax casting method by using a wax pattern of the desired component. However, the recent development of CAD/CAM pattern design and 3D rapid prototyping allow the manufacturing of complex shapes with high difficulty to be obtained by other processes with removal material like polymers with low melting point.²³

The as-cast method of fabrication leads to poor mechanical properties compared with new fabrication procedures.^{6,24,25} Generally, the microstructure of the as-cast products consist of a cobalt-rich matrix (α phase) with an FCC (face-centred cubic) structure. It is well known that the main defects present in the as-cast state are: porosity, chemical inhomogeneity, large grain size and a microstructure with hard precipitates in the interdendritic zones.²⁶ Also due to the casting process, inhomogeneities in carbide morphology and their size and distribution can strongly influence implant properties. However, the mechanical properties can be improved with ulterior heat treatments by dissolving the large carbide network and producing a more homogeneous structure.

Pure Co undergoes an allotropic transformation at 690 K from the high- temperature γ -phase with the FCC structure to the low- temperature ϵ -phase with the HCP (hexagonal close-packed) structure.²⁷ This transformation is shear dominant with thermal hysteresis; therefore, it has been classified as martensitic and is closely related to the microstructure and mechanical and chemical properties of the Co-based alloys. The transformation temperature is changed by the addition of alloying elements to Co. Biomedical CoCr alloys contain more than 20% m/m of Cr, which improves the corrosion resistance by forming a passive layer consisting mainly of Cr oxide. The addition of Cr increases the transformation temperature (Figure 2A). The transformation temperatures in Co-20mass%Cr and Co-30mass%Cr alloys are approximately between 1100 and 1200 K, respectively.

Alloying elements influence the temperatures of the HCP to FCC transformation of Co alloys²⁸ (Figure 2B); note the effect of molybdenum and chromium addition on the temperature change with respect to pure Co per 1% of the alloying element. The vertical axis shows the solubility of the alloying element in FCC Co. Cr are HCP stabilizers.

Selective laser melting (SLM) has received a great deal of attention in recent years and its use is increasingly for the fabrication of customized dental components made of CoCrMo.^{5,6} Regarding the microstructural properties, Zhang *et al.*,²⁹ observed that SLM-fabricated CoCrMo alloy has a mixture of γ -phase and ϵ -phase, with predominantly γ -phase. They also found that long heat treatment time (10h) and high aging temperature (900°C) promoted the martensitic transformation ($\gamma \rightarrow \epsilon$) and precipitation, which enhanced the microhardness.

In addition, Song *et al.*,²⁴ demonstrated that the heat treatment caused an increase in the tensile strength and elongation of the SLM-fabricated parts besides reduced yield strength and hardness.

España *et al.*,³⁰ established that the implementation of methodologies to reduce CoCrMo alloy stiffness while maintaining its wear resistance and biocompatibility are extremely important. In this context, they have used laser engineered net shaping (LENS™) technology and successfully fabricated net shape porous CoCrMo alloy structures without compromising its biocompatibility for bone implant applications, creating a fully dense outer surface to retain its wear resistance and a porous core inside the structure, reducing the effective stiffness of the structure to match that of human cortical bone. Mantrala *et al.*,²⁵ found that the coatings fabricated using high laser power, low powder feed rate and high scan velocity, provide the highest hardness and wear resistance; on the contrary, the corrosion resistance was higher for the coatings fabricated using lower levels.

Properties of CoCrMo Alloys

Mechanical Properties

As mentioned before, the mechanical properties of implants mostly depend on the microstructural characteristic such as the quantity, distribution and morphology of hard phases, which depend on the processing conditions. Cobalt is the major element in the alloy and its content is regarded for the elastic modulus, strength and hardness³¹ (Table 2).

The other main feature of Co-based alloys is the presence of carbon, forming carbides, whose distribution and size are influenced by the manufacturing process. The two principal types of carbides are $M_{23}C_6$ (M=Cr, Mo, Co) and M_7C_3 (Figure 3).^{5,27,29,31}

The grain sizes are large in casting alloys; this is a significant limitation since it decreases the tensile strength of the alloy. Molybdenum is added in order to produce finer grains, which results in higher tensile strengths and also improves the ductility, but decreases the elongation and workability of CoCrMo alloys.^{27,33} However, it increases the solidification range and changes the morphology of the precipitates by segregation generating additional quantities of eutectic carbides.³⁴ Overall, the volume fractions of alpha and carbide phases are about 85% and 15%, respectively. A finer distribution of carbides has a hardening effect.³⁵

Chromium is the second major element in the alloy

and is responsible for its tarnish and corrosion resistance. The chromium content on a CoCrMo alloy should not exceed 30% because it increases the difficulty to cast. Another point related with this percentage threshold of chromium is that the alloy starts to form a brittle phase known as sigma phase.³⁶

The addition of zirconium (Zr)³⁷ can yield a fine microstructure of the as-cast materials, resulting in increased tensile strength and elongation, showing maximum values at 0.01% Zr and over-added Zr content (over 0.37%) exhibits a detrimental effect on the mechanical properties of the alloy, except for hardness. On the other hand, the addition of nitrogen to CoCrMo alloys increases their mechanical strength.^{38,39}

Better elongation and workability were achieved in the alloy with a nitrogen content of 0.10% of its mass, where the γ -to- ϵ martensitic transformation was completely suppressed. However, further addition of nitrogen was reported to slightly decrease the elongation to failure because of the enhanced formation of annealing twins.³⁹

Corrosion and Electrochemical Properties

Due to their particular electronic structure characterized by the presence of free electrons in the crystalline network, metals and alloys react chemically or electrochemically and thus may suffer corrosion processes.⁴⁰ All forms CoCrMo alloys are exposed to aggressive conditions in the oral cavity that represents an ideal environment for metallic ion release and biodegradation.⁴¹ The metallic ions released from dental materials can cause local and/or systemic adverse effects in the human body. Therefore, dental materials are required to possess appropriate mechanical, physical, chemical and biological properties.

With variations in the carbon concentrations, precipitates, and microstructures, the dominant corrosion protection comes from its bulk composition and from the formation of a chromium oxide layer on the surface.^{39,40,42-44} The thin oxide layer of approximately 2nm in thickness is a mixture of Co and Cr oxide, primarily of Cr_2O_3 with small amounts of Co_3O_4 and $MoOx$.

This oxide film protects properly heat-treated CoCrMo alloys from intergranular corrosion and crevice corrosion attack and can improve the biocompatibility and wear resistance.³¹ Zeng *et al.*,⁴⁵ determined that the film was Cr oxide, but the oxide was not crystalline Cr_2O_3 as often assumed; they also observed the in vivo behaviour of the oxide layer and concluded that the thickness varied

considerably over small distances, reflecting changes resulting from the fretting contact.

Generally, the stronger and the more stable the passive oxide film is on the CoCrMo implant alloy, the better the corrosion resistance and also the lesser the release of the metallic ions from the implant alloy.⁴⁵ However, care should be taken during component manufacture to ensure low porosity levels, uniform grain structure and free from shrinkage cavities. Lower percentage of Carbon in the chemical composition of the bulk alloy and thermal treatments favour the homogenization of the surface (less amount of carbides), thus increasing the availability of Cr to form the oxide film and improving the corrosion resistance of the alloy.⁴⁶

On the contrary, results from Cawley *et al.*,⁴⁷ suggest that the as-cast microstructural condition with the highest carbide volume has the lowest wear, and they also found a correlation between carbide volume fraction and wear-rate with the highest carbide volume fraction giving the lowest wear-rate. Jenko *et al.*,³¹ established that the surface should be free from local reduction of the Chromium concentration in the surroundings of the Cr₂₃C₆ carbides, since it could conduce to the initiation of the corrosion mechanism on the surface of the CoCrMo alloy (Figure 4) and they confirmed this finding with further recent studies.³¹

In addition, the alloy microstructure also plays a crucial role on the general electrochemical behaviour as demonstrated by Guo *et al.*,⁴⁸ Muñoz *et al.*,⁴⁸ and Wang *et al.*⁵⁰ The mechanism of material degradation is influenced by both mechanical factors and the electrochemical behaviour of the individual material.¹⁵ Electrochemical corrosion represent destructive attack on metals or alloys exercised by the corrosive environment through electrochemical reactions, in which the metal releases electrons and its positive ions get into solution. The formation of positive ions and electrons create an electrical potential (in volts) called corrosion potential.⁴⁰

In this context, Aslan *et al.*,⁵¹ proposed that the passive Cr₂O₃ layer on CoCrMo implant alloys behaves as an efficient barrier to corrosion, and increases the resistance to charge transfer at the corrosion interface. Yanet *et al.*,¹⁵ established that under a positive potential, the CoCrMo alloy exhibited a decrease in wear loss and low friction coefficient. This is due to the formation of complexes on the material surface to lubricate the counter bodies and to act like a barrier to corrosion, and they postulated that a possible way to reduce material degradation is by

enforcing a positive potential in the passive region.

It clearly proves that by forcing the passive film and organometallic complexes to form, wear, corrosion and tribocorrosion resistance of materials could be improved. Bedolla,⁵² Rodriguez-Castro⁵³ and Hernandez-Rodriguez *et al.*,⁵⁴ found that the boron addition improved the wear resistance by refinement in grain size and a homogeneous distribution of hard precipitated along the matrix. Additionally, other authors have investigated the effect of surface treatments such as diamond-like carbon (DLC),⁵⁵⁻⁵⁷ carbon ion implantation⁵⁸ and TiO₂ coating^{59,60} on CoCrMo alloys to reduce the corrosion of implant alloys, obtaining good results.

Biocompatibility and use of CoCrMo alloy for bone therapies

CoCrMo alloys are regarded as highly biocompatible materials and have been employed in the fabrication of prostheses since the 1940s because of the effectiveness in restoring lost function of human bone under high loads. However, the mismatch of the Young's modulus between bone (10–30 GPa) and the CoCrMo alloy (248 GPa) lead to stress-shielding, which causes bone resorption around the implant and reduces the lifespan of the implant.³⁰

In order to overcome this drawback, the development of porous implants through Additive Manufacturing (AM) techniques has been proved to be a solution.⁶¹ The porosity enables to lower the mechanical properties towards those of bone; and also, the bone ingrowth around the implants is improved by colonization of pores by living cells.⁶²

In addition, when an implant material is attached to bone and is exposed to cyclic loads, relative movements at the interface cause wear stress due to the difference of Young's Modulus between the bone and the implant. Therefore, wear resistance is crucial for implant materials.⁶³ On the other hand, corrosion damage is also a very important issue for metallic implants, because it can affect the biocompatibility and mechanical integrity of implants.⁶⁴ Generally, the initial corrosion ions produced when the passive film is damaged are reported to be Co₂+ and Cr₂+ species in acidic conditions and CoO and CrO at neutral pH, respectively.^{65,66} Wear and corrosion products of the CoCrMo alloy have been associated with local and systemic side effects such as erythema,⁶⁷ inflammation,^{16,68} osteolysis,⁶⁹ toxicity⁷⁰ and hypersensitivity.¹⁷ The formation of solid corrosion products (predominantly consisting of metal oxides and hydroxides) may trigger local biological reactions in the

human body, leading to accelerated bone resorption and eventually bone loss.¹⁶ Because of that, CoCrMo biocompatibility is closely linked to the high resistance against corrosion due to the spontaneous formation of the passive oxide film, the integrity of which has been strongly correlated to the chemical and mechanical stability of implants⁴⁶ as previously described. Armstead *et al.*,⁷¹ performed an *in vitro* study in which at low concentrations (*i.e.* 0.1 and 1 µg/mL); nano- and micro-CoCrMo particles did not cause significant toxicity to osteoblasts and macrophages.

Typically, cells may isolate small amounts of foreign particles in internal phagolysosomal compartments, which could restrict them from further interacting with other cellular components thereby preventing extensive cellular toxicity;⁷² this cellular mechanism seems to support the high biocompatibility of CoCrMo alloys in orthopaedic settings.

After biomaterials are implanted into the human body, there are unavoidable interactions between the biological environment and implant surfaces. Proteins and other biological substances come in contact with the foreign surface immediately, and proteins are one of the main factors that modulate the longer term cellular and/or encapsulation response. For some metallic materials, proteins were found to be able to adsorb onto the material surface and reduce the corrosion rate;⁷³ however, other authors⁷⁴ found that surface proteins could promote the corrosion process for CoCrMo alloys. On the other hand, on some metal and alloy surfaces, an accelerated metal ion release rate was observed.⁷⁵ Therefore, there is a need to fully understand the role of proteins and adsorbed-protein layers in metallic materials and, specifically, in CoCrMo. Several authors have studied the combination of corrosion and wear particles with proteins and/or amino acids and their effect in the body. Yan *et al.*,¹⁵ reported in an *in vitro* study, that due to the fact that proteins carry a net negative charge at pH between 7.2-7.8, it is likely that more proteins were attracted to the sample surface by electrostatic forces and bind through the released metal ions.

They concluded that proteins and/or amino acids could influence the material corrosion behaviour in static conditions and tribocorrosion behaviour in biotribocorrosion systems. In addition, the carbon content of the alloy may influence the corrosion rate and material degradation in terms of proteins and amino acids biofilm formation.⁵⁸ Sun *et al.*,⁷⁶ further studied the effects of

protein adsorption on the sliding-corrosion and abrasion-corrosion performance of a cast CoCrMo. They reported that the pH of the surrounding environment controls the charge of proteins, which will subsequently affect the protein adsorption and therefore influence the mechanical degradation of the alloy during the tribocorrosion process. When the CoCrMo surface was exposed to a more electropositive potential, the negatively charged protein has a greater tendency to be attracted towards the surface.⁷⁶

Zhang *et al.*,⁷⁷ proposed that the biocompatibility of the bulk CoCrMo alloy is unqualified due to its inadequate capability of triggering new bone tissue formation and osseointegration around implants. In this context, several techniques (Table 3) have been reported to improve the biocompatibility of the CoCrMo alloy to promote the attachment, proliferation and guided differentiation of seeding cells.

Some of these techniques are still ineffective and unsatisfactory in order to improve osseointegration or bone formation or are unlikely to be commercially viable due to scale-up issues; however, there are some successful efforts that should be further studied and tested *in vivo*. In this context, Decco *et al.*,⁸⁴ have demonstrated that the placement of an osteoconductive non-resolvable membrane of CoCrMo alloy favours osseointegration, blood supply to the site provides growth factors; and these factors may be sufficient elements to achieve bone augmentation in a period of three months in rabbit tibia.

The same year, these authors established that the combination of the membranes with platelet-rich plasma (PRP) stimulated bone augmentation at the application site and that extremities with PRP showed higher angiogenesis at 60 days, which might indicate higher proliferation and cellular activity. In addition, they observed twice as many osteoblasts in the tibia treated with PRP compared to whole blood at the same period of time.⁸⁵ Recently, the same research group concluded that bone augmentation has been accomplished just by providing the tissue an adequate space using the CoCrMo membranes alone.⁸⁶ This might lead to the exercise of less traumatic augmentation techniques by decreasing tissue response to bone grafts.

In a canine model, Stenlund *et al.*,⁸⁷ observed less bone around CoCr-based implants compared with Ti6Al4V implants, but it was suggested that this observation could be due to the difference in the stiffness of the

materials rather than the difference in surface chemistry.

Shah *et al.*,⁸⁸ evaluated the osseointegration of 3D printed CoCrMo porous scaffolds prepared by electron beam melting with Ti6Al4V as control. They demonstrated the achievement of bone ingrowth around and inside open-pore CoCrMo substrates comparable to that of Ti-alloy, even though Ti6Al4V showed the highest total bone-implant contact (BIC). They also observed that osteocytes were in direct contact with the CoCrMo surface, with a higher osteocyte density in the periphery of the porous network. Recently, they analysed the addition of zirconium to the 3D printed CoCrMo implants and how it influenced the bone osseointegration.⁸⁹

They observed bone ingrowth into surface irregularities of 3D printed CoCrMo and CoCrMo+Zr implants with an evident and extensive remodelling and osteocytes attached directly to the implant surface. The interfacial tissue at both implants has similar mineral crystallinity, apatite-to-collagen ratio, Ca/P ratio and BIC, among other parameters, indicating that the bone tissue adjacent to both implant types was highly mature and healed at similar rates.

These potential uses of CoCrMo alloy have reported good results, providing sufficient space for the promotion of bone regeneration; however, it has not been documented in any clinical report yet. Due to the non-degradable nature of this alloy, during the temporary reconstruction and after the healing process, the implants usually need to be removed through a second surgery with potential complications such as infection, nerve damage, risk of bone re-fracture and increased pain at the site of surgery.⁹⁰ Moreover, metallic implants can cause soft tissue irritation, growth disturbance, stress shielding and bone loss.

CONCLUSION.

Several mechanical properties can be improved by the coating of the CrCoMo implants with bioactive materials, or by the addition of alloying elements to the bulk composition, regardless of the manufacturing method. However, most processes adversely affect other properties and the implant outcomes.

Although some poor mechanical properties of the CoCrMo alloy still remain, its biocompatibility is suitable; thus, in applications on which implants do not have to support large loads or when the implant geometry is not exposed to loads in its principal axis

such as for vertical bone augmentation, this drawback is not a limitation.

Cell culture studies indicated that the SLM, MPS, nanophase topography, SLA250, and surfaces with coatings of graphene, DLC, TiO₂ and Nb-HA resulted in enhanced cell adhesion and proliferation. In addition, increased osteoprogenitor cell differentiation was reported in SLA250 surfaces and TiO₂ coating; though, some modified surfaces did not show any differences to the standard CoCrMo alloy, as the HA-TiN coating. Although only a few studies have evaluated the *in vivo* performance of the CoCrMo alloy in the context of bone regeneration and repair, they have shown that this alloy favours osseointegration.

Further, bone formation patterns were comparable to those observed in Ti-alloys demonstrating the biocompatibility of the CoCrMo.

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