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1 **Combining bioresorbable polyesters and bioactive glasses: orthopedic applications of composite implants and bone**
2 **tissue engineering scaffolds.**

3

4 Lukas Gritsch^{1,2}, Eloïse Perrin^{3,4,#}, Jean-Marc Chenal³, Yann Fredholm^{4,†}, Anthony LB Maçon⁴, Jérôme Chevalier^{3,*} and
5 Aldo R Boccaccini^{4,*}

6 **Affiliations**

7 ¹ Institute of Biomaterials, University of Erlangen-Nuremberg, Cauerstraße 6, 91058 Erlangen, Germany

8 ² Université Clermont Auvergne, CNRS/IN2P3, Laboratoire de Physique de Clermont, 4 Avenue Blaise Pascal, 63178
9 Aubière (Clermont-Ferrand), France

10 ³ Université de Lyon, INSA de Lyon, Université Claude Bernard Lyon 1 – UMR CNRS 5510 MATEIS, 7 Avenue Jean
11 Capelle, 69621 Villeurbanne cedex, France

12 ⁴ Noraker, 13 Avenue Albert Einstein 69100 Villeurbanne France, France

13

14 # Now at: Becton Dickinson France SAS, 11 Rue Aristide Berges, 38800 Le Pont-de-Claix, France

15 † Now at: BSI group, Davy Avenue Knowlhill, Milton Keynes MK5 8PP, United Kingdom

16

17 *** Corresponding authors**

18 Aldo R. Boccaccini, e-mail: aldo.boccaccini@ww.uni-erlangen.de

19 Jérôme Chevalier, e-mail: jerome.chevalier@insa-lyon.fr

20

1 **Abstract**

2 This overview showcases the current state of the art in the fabrication, properties and applications of bioactive glass-
3 polyester composites for dentistry, craniomaxillofacial surgery, orthopedics and bone tissue engineering. The combination
4 of these materials is a successful strategy to simultaneously modulate and optimize the degradation rate, mechanical
5 properties, cell response and osteostimulation of bone substitutes. In particular, two major approaches can be identified:
6 bone regeneration or bone repair. The first is performed using porous scaffolding materials, the second one by using dense
7 molded implants. For both strategies, the synthesis, processing and characterization of materials are presented based on a
8 comprehensive review of the available literature. Relevant recent *in vitro* and *in vivo* studies are also covered. Current and
9 future applications of this interesting family of biocomposites are discussed. The literature search revealed a considerable
10 body of work investigating the biological performance of these composites, evidencing the interest on the topic. In
11 particular, the use of polyester/BG composites is well-studied in terms of material fabrication, as well as characterization of
12 physicochemical and in vitro biological properties. On the other hand, there is much less evidence of translational research
13 efforts. It is apparent that future research will have to focus on the collection of more in vivo and clinical data to broaden
14 the knowledge of the performance of these materials in realistic conditions.

15

16 **Keywords**

17 Bioresorbable polyesters, Bioactive glasses, Composites, Orthopedics, Scaffolds

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1 **1. Introduction and scope**

2 Traditionally, biomaterials can be divided into three generations (Figure 1). The first generation was focused on the
3 development of materials with the lowest biological reactivity (i.e. bioinert). These are mostly metal alloys or structural
4 ceramics, biomedical materials that are widely used for permanent orthopedic implants thanks to their mechanical
5 performances and long-term reliability [1]. Wear [2–4], fatigue fracture [5,6] and postoperative infection [6] are major
6 issues tackled by research in the field. In addition, the high stiffness of such metals and ceramics compared to bone leads to
7 stress shielding [1], which is a change in stress distribution between the implant and bone and in the most severe cases may
8 lead to bone degradation and aseptic loosening [7]. The emphasis on bio-inertness started to shift towards bio-integration
9 during the late 1960s [8], when Professor Larry Hench started a systematic research into bioactive glass (BG), discovering
10 that it was possible to synthesize inorganic materials that could actively elicit a desired response in vivo, leading to a strong
11 bonding between bone and a synthetic material prompted by chemical and biological reactions occurring at the BG surface
12 [9]. A second generation of biomaterials, whose goal was “bioactivity” (often defined as the ability to form a calcium-
13 phosphate layer at their surface in the presence of body fluids), started to shape up: BGs were initially used in medical
14 applications as monoliths (e.g. middle ear implants) and in the form of granules (i.e. to fill bone defects) [10]. In
15 subsequent research, BGs were found to successfully stimulate the regeneration of bone [11,12]. Applications of BGs in the
16 field of bone tissue engineering were then proposed [11,13]. BGs have also been synthesized in a wide range of
17 compositions, with tailored physicochemical and biological properties according to the need. However, BGs, as most of
18 bioactive inorganic materials, are too brittle to support most of the stress that bone is subject to [14–16]. In addition,
19 shaping of bioactive glasses towards complex shapes (e.g. 3D scaffolds) is difficult and highly composition-dependent.

20 During the second biomaterial generation, advances in polymer chemistry also led to the development of novel polymer
21 structures with controllable mechanical and degradation behavior under physiological conditions [17]. Since the
22 introduction of the biodegradable suture material Dexon[®] (poly(glycolic acid), PGA) [18,19], bioresorbable polymers have
23 grown in importance and are widely used in orthopedics and traumatology as fracture repair devices, in the pharmaceutical
24 industry as drug delivery devices and, most recently, as scaffolds for tissue engineering [18,20–23]. Poly(α -hydroxy acids)
25 are the predominant group of bioresorbable polymers mainly because of their attractive mechanical properties, and also for
26 their controllable bioresorbability and biocompatibility. Amongst them, poly(lactic acid) (PLA), poly(glycolic acid) (PGA)
27 and poly(ϵ -caprolactone) (PCL) are thermoplastic polymers that can be processed in a great variety of sizes and shapes by
28 conventional plastic processing methods, including extrusion, injection molding and fiber spinning. They have an extensive
29 FDA clearance history in a wide range of application as wound closure items (e.g. sutures), implantable devices (e.g.
30 screws, pins, bone anchors), and drug delivery systems, which include microspheres, fibers, films, rods and others [18].
31 However, bioresorbable polymers still have some disadvantages in clinical practice: although the bending strength of
32 polyester is enough in some devices, its rigidity is relatively low in comparison to natural cortical bone and should be
33 increased [16,24–30]. In addition, biodegradable polymer devices can break during implant insertion [31] and their
34 degradation products can cause foreign-body [32,33] and inflammatory [34–37] reactions, probably due to the acidic nature
35 of the byproducts [38,39]. The lower pH can also hinder the precipitation of hydroxyapatite on the device surfaces [40],
36 failing to promote bone growth while degrading and leaving non-functional and non-mineralized fibrous (scar) tissue [41–
37 49].

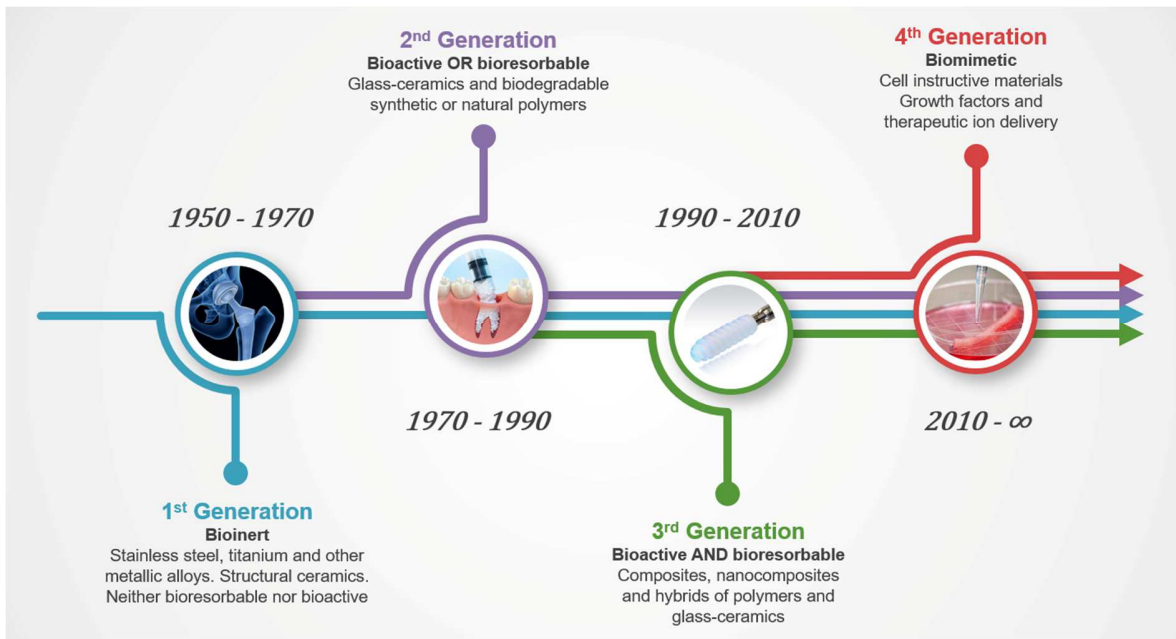


Figure 1: The generations of biomaterials for bone substitution, repair and regeneration.

The limitations of the second generation biomaterials were addressed with the development of a third generation of biomaterials, characterized by functional tissue regeneration and biomimicry as goals. The properties of bioactivity and bioresorbability started to be combined into composite structures to overcome the limits biopolymers and bioceramics taken separately in order to meet the complex and interlaced set of requirements, advancing from bone substitute materials to bone regeneration. Such bioactive materials should be biomechanically stable, biocompatible, non-toxic and with a highly favorable benefit-to-risk ratio. They should stimulate the natural bone regenerative mechanisms by containing inductive factors to promote bone healing. Furthermore, they should be gradually replaced by healing bone, with a controlled *in vivo* dissolution rate, resorbing at a rate equal to that of bone formation. At the same time, the material should be able to exert an antibacterial effect on the host tissue. Additionally, it should be easy to use and readily available [50], with adequate mechanical properties to share load with bone and avoid stress-shielding [16]. In case the material is used as a three-dimensional and permeable scaffold to guide bone regeneration, it should also be processable into a structure that mimics the 3D architecture of natural bone [16].

Table 1: Summary of the mechanical properties of bone. Reported from references [16,51,52].

Material	Compressive strength (MPa)	Tensile strength (MPa)	Young's modulus (GPa)	Flexural strength (MPa)	Flexural modulus (GPa)	Elongation (%)	Ref.
Trabecular bone	1 - 16	7.4	0.1 - 0.5	-	-	-	[16,51]
Cortical bone	130 - 200	50 - 151	7 - 30	90 - 280	3 - 14	5 - 15	[16,51,53,54]

1 The need of novel biomaterials to fabricate bone grafting substitutes and temporary orthopedic devices is ever growing,
2 proportionally to the constant increase in incidence of bone fractures and other bone defects. While the use of autologous
3 bone grafts and allografts is still a suitable treatment, synthetic bioactive composites offer significant advantages in terms
4 of scalability, safety and availability. The lower biomimicry of synthetic devices is outbalanced by the possibility of high
5 throughput production that could meet the current demand for functional grafts. As a matter of fact, the orthopedic sector is
6 experiencing a significant unmet supply. This demand is hard to meet via naturally sourced grafts alone and opens up a
7 budding market opportunity for new technologies. As for 2014, the annual cost of bone defect repair was estimated around
8 \$2.5 billion, of which circa \$1 billion was the direct cost of the implanted materials, of which circa 30% was synthetic bone
9 grafts [55,56]. This figure is expected to only increase with time, due to population aging and overall increase, urging the
10 scientific community to come up with new solutions to help orthopedic patients.

11 Among other established biomaterials technologies explored to reach this goal, organic/inorganic composites prepared
12 dispersing a bioactive particulate phase of BG within a poly(α -hydroxy acid) matrix are one of the most reliable and
13 explored technologies and an extensive body of scientific literature is available, including previous reviews [57,58] as well
14 as a variety of successful commercial products (see for example NovaBone, BioGran[®] and BonAlive[®] [10]). Such
15 composites reach one of the best approximations of the mechanical properties of bone (Table 1) while simultaneously
16 offering bioactivity, osteoconductivity, angiogenic effect, antibacterial activity and osteostimulation thanks to the presence
17 of BG. The polymer matrix on the other hand provides high resilience and processability, allowing thermoplastic
18 processing into complex shapes. The combination of bioresorbable polymers and BGs in composites started to be
19 investigated about 20 years ago [57,59], and was introduced as a promising strategy in order to balance their shortcomings,
20 creating beneficial interactions in terms of improved mechanical properties (i.e. brittle BG balancing out the lack or rigidity
21 of polyesters) and biocompatibility (i.e. if properly tailored, the opposite nature of the degradation behavior of the two
22 materials may counterbalance each other creating a neutral pH buffer [60,61]). Thanks to the silica content which enhances
23 osteogenesis and angiogenesis, BGs generally showed equal or better results [62–69] than HA or β -TCP [70–72] when used
24 as fillers. When tested clinically, results showed that the incorporation of a mineral phase in a polymer matrix could
25 modulate the degradation rate and enhance the mechanical properties, cell adhesion and osteostimulation [41,73,74].

26 In this review, we offer a retrospective on the wide family of polyester/BGs composite materials, their requirements and
27 success in orthopedics and tissue engineering, focusing on their fabrication into porous scaffolds or dense molded implants,
28 their properties and applications. Relevant processing and characterization techniques will be discussed, first for tissue
29 engineering scaffolds and then for molded bulk implants. The current knowledge on bioactive glass-polyester composites
30 will be described in terms of their key mechanical and *in vitro* and *in vivo* biological properties. Finally, a brief outlook on
31 the future development of such composites to enter the fourth generation of biomaterials (Figure 1) will be presented.

32 **2. Bioactive glasses**

33 Named after their ability to trigger a specific biological response when in contact with body fluids, bioactive glass in its
34 well-first and well-known 45S5 Bioglass[®] formulation, was the first man-made inorganic material able to interact and bond
35 with host bone tissue [75]. Once implanted, 45S5 BG progressively degrades and induces the formation of a bone mineral-

1 like structure that is then colonized and ultimately produces new bone [75–77]. Since 1993, BGs have mainly been used as
 2 bone grafts granules for dental, orthopedic, cranio- maxillofacial and spinal surgery [7,76,78].
 3 Bioactive glasses can be synthesized through traditional melt quenching or via sol-gel chemistry. Generally speaking, a
 4 broad spectrum of different formulations and physical properties can be obtained by appropriate choice of chemical
 5 composition and processing method. For instance, sol-gel glasses have inherent meso- and nano-porosity, offering large
 6 surface areas ideal for drug delivery. The two BG production processes and their unique characteristics are described and
 7 discussed in detail in the literature [10,15,65]. Regardless of the process used, the strength of bioactive glasses is the
 8 possibility to radically change their properties by changing the formulation (Table 2), in particular the choice of
 9 composition has a strong effect on the degradation and mechanical behavior of the final material by modifying the network
 10 connectivity (NC) of the glass [79–81].

11 **Table 2:** Name, composition (%mol), network connectivity and elaboration process of some bioactive glasses. For more information,
 12 refer to references [65,73,81–86] (Key: MD = melt derived, SG = sol-gel, * = MgO considered as network modifier).

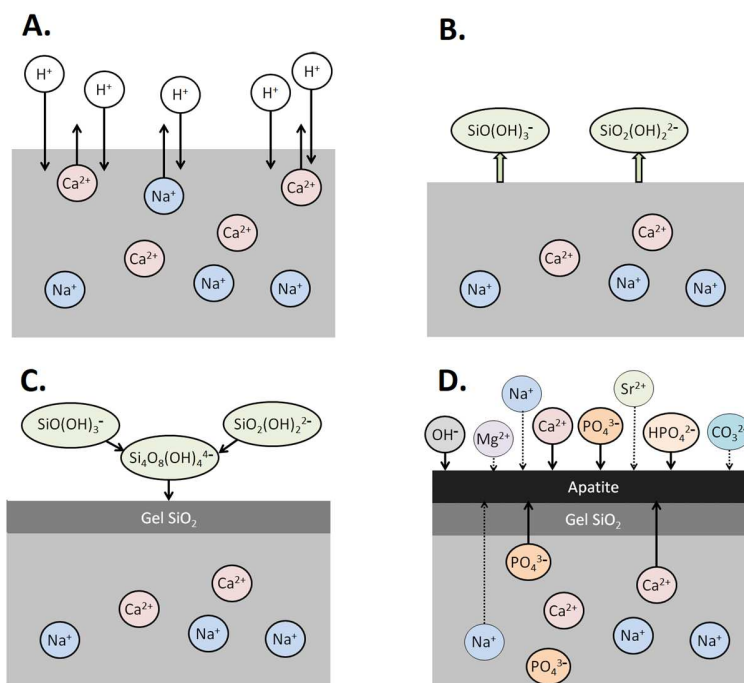
Glass		Composition in molar fraction (%mol)							NC	Process
Name	Commercial names	SiO ₂	CaO	Na ₂ O	P ₂ O ₅	K ₂ O	MgO	B ₂ O ₃		
45S5	(Bioglass [®] , PerioGlass [®] , Novabone [®] , Biogran [®] , Novamin [®] , GlassBONE [®] , Activioss [®])	46.1	26.9	24.4	2.6	0	0	0	2.12	MD
S53P4	(BonAlive [®])	53.8	21.8	22.7	1.7	0	0	0	2.54	MD
13-93	-	54.6	22.1	6.0	1.7	7.9	7.7	0	2.59*	MD
ICIE4	-	49.5	42.8	6.6	1.1	0	0	0	2.11	MD
S68	-	67	9	13	1	0	8	2	N/A	N/A
0106-B1		37.5	22.6	5.9	4.0	12.0	5.5	12.5	N/A	MD
60S	-	60	34	0	6	0	0	0	N/A	SG
58S	-	60	36	0	4	0	0	0	N/A	SG
P40B10	-	0	16	10	40	0	24	10	N/A	MD
47.5B	-	47.5	20	10	2.5	10	10	0	N/A	MD

13 The mechanical properties of BGs are usually considered sufficient for most conventional bone grafting procedures, as the
 14 application of inorganic biomaterial fillers is typically instrumented (i.e. metal fixation is used): the bone defect is filled
 15 with a bone graft that is intended to fill the space in the first weeks/months from implantation and aid regeneration without
 16 providing considerable mechanical support [16]. In parallel, the fracture toughness, tensile/flexural strength and
 17 processability into complex shapes remain limiting factors for the development of porous BG structures [14–16,87,88].
 18 Additional toughening processing is required to obtain adequate properties, especially in porous BG scaffolds [89]. For
 19 instance, scaffolds produced by foam replica have been toughened by changing the original template from polyurethane
 20 foams to natural marine sponges [90]. The authors reported that there was inverse proportion between the percentage of
 21 total porosity and the compressive Young's modulus of the scaffolds [90]. Alternatively, highly porous BG scaffolds can be
 22 toughened by coating and infiltrating with biodegradable polymers [91,92]. When these strategies failed to provide
 23 sufficient mechanical strength, research found a solution in the fabrication of composite materials combining BGs with a

1 polymeric matrix: as it will be addressed in this review, this approach preserves the beneficial biological properties of BG
 2 while simultaneously expanding the range of mechanical properties and the number of processing techniques available.

3 In terms of biocompatibility, the general consensus is that BGs do not pose a threat to the organism [64,65,73,93–110]. In a
 4 relevant investigation [111], granules of about 300 μm were resorbed at a rate similar to the one of bone regeneration, with
 5 complete healing observed after 12 months of implantation in a human sinus lift. Studies have ruled out the risk of silicon
 6 accumulation in kidneys, liver, heart, brain, lymph nodes, thymus spleen and lungs [112,113]. Some BG have been also
 7 shown to have antibacterial effects when clinically applied thanks to ion release and local alkalinization (especially when
 8 coupled with therapeutic ions) [10,114–118]. Some in vitro reports, on the other hand, indicate that alkalinization could
 9 result in apparent cytotoxicity, which is clearly manifested in in vitro studies [10,114–116]. To avoid it, a preconditioning
 10 step in a proper buffer solution (e.g. PBS – Phosphate Buffered Saline) is recommended in laboratory practice whenever
 11 assessing the cell compatibility of BGs, which avoids an excessive, possibly cytotoxic, pH increase, as recently described
 12 in a comprehensive review [119].

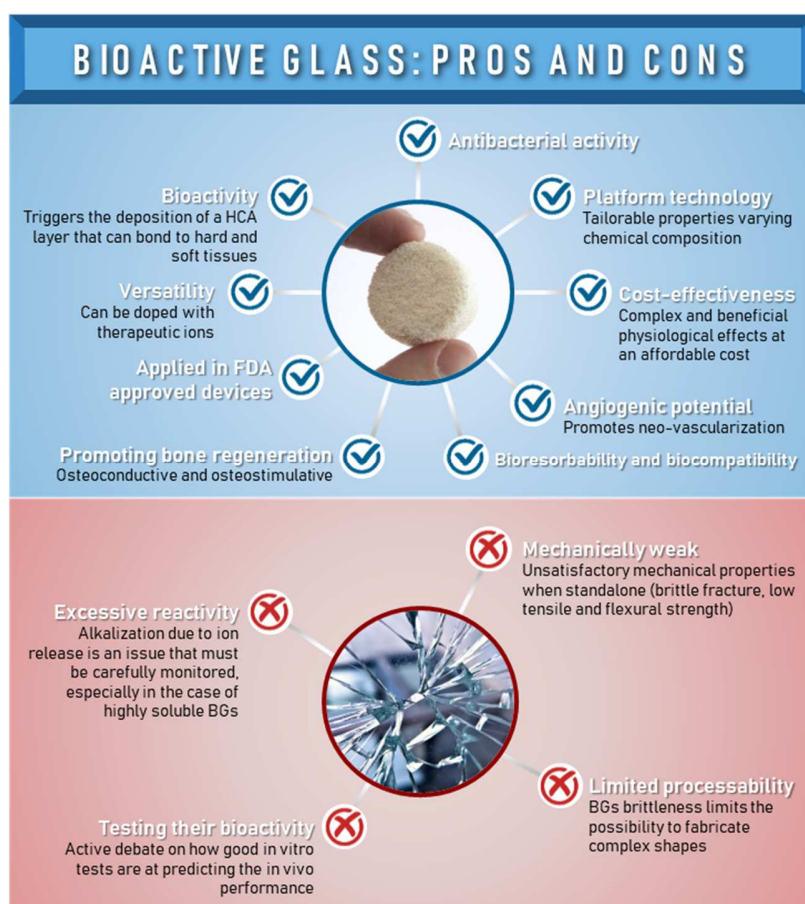
13 The defining property of BGs is their ability to bond to bone which usually take place through the deposition of a calcium
 14 phosphate layer at the interface between the implanted material and the tissue. In the context of bone replacing materials or
 15 bone tissue engineering scaffolds, this property is referred to as “bioactivity”. The calcium phosphate layer has a
 16 hydroxycarbonated apatite (HCA) crystalline structure very similar to the physiological mineral phase of bone [65].
 17 According to Hench et al. [120], HCA formation in silicate bioactive glasses is the result of a complex series of reactions
 18 between the glass surface and the biological environment, which leads to the progressive release of therapeutic ions in the
 19 environment surrounding the implant and their subsequent precipitation as HCA (Figure 2) [121].



20
 21
 22

Figure 2: Mechanism of HCA formation on the surface of a bioactive glass in contact with body fluids. Picture courtesy of Dr. Cédric Bossard.

1 Since bioactivity is linked to the dissolution rate of the material, BGs with high NC tend to be less bioactive than BGs with
 2 lower NC. Thanks to their higher reactivity and biomimicry, bone anchoring is generally faster for BGs compared to the
 3 one achieved by conventional calcium phosphate grafts [122,123]. In addition, BGs can release osteostimulative ions
 4 during dissolution. Several studies report the beneficial contribution of Ca^{2+} , Si^{4+} and P^{5+} ions on osteoblast proliferation
 5 and differentiation [62,65,66], collagen formation [124,125] angiogenesis [124,126] and growth factor upregulation
 6 [63,64,69]. Bioactivity is usually assessed by performing an assay in Simulated Body Fluid (SBF), a standardized saline
 7 solution (ISO 23317:2012) replicating the concentration of ions in human plasma usually prepared following the protocol
 8 introduced by Kokubo *et al.* [127]. Specimens are incubated at physiological temperature usually up to 28 days [59,61,128–
 9 133] and the deposition of HCA is assessed and quantified. Longer-term SBF studies are also reported [134,135]. It is
 10 important to note that the *in vitro* formation of HCA and the actual *in vivo* bond to bone are not always correlated and there
 11 is still debate on whether SBF assays can predict *in vivo* bioactivity [127,136–138]. The debate on the topic has been
 12 popular in the past decade [138] and it is still open to date, with several papers discussing whether bioactivity can or cannot
 13 be tested in vitro with SBF solution. Recently, Zadpoor [137] did a systematic review of studies investigating the *in vitro/in*
 14 *vivo* trade-off, reporting that SBF assays are in fact quite coherent with *in vivo* outcomes in most cases. Advantages and
 15 challenges in the use of BGs are summarized in Figure 3.



16

17 **Figure 3:** Advantages and drawbacks of bioactive glasses for biomedical applications (with focus on bone replacement/bone repair).

1 3. Bioresorbable polyesters

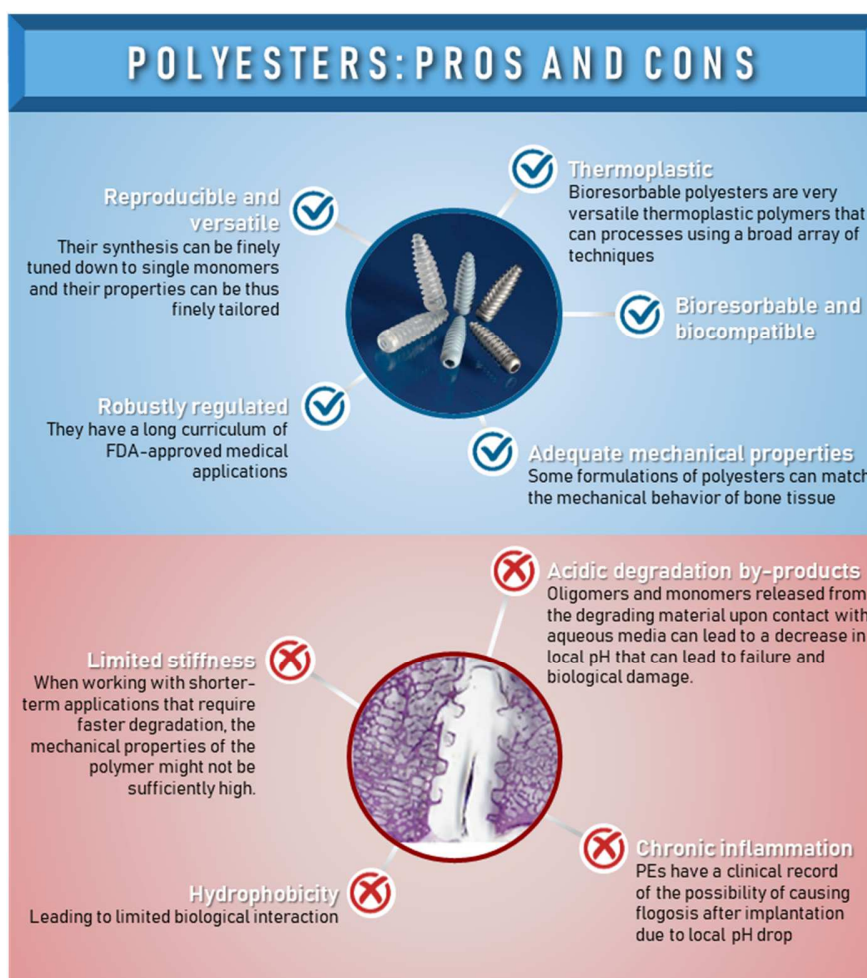
2 Bioresorbable polyesters have been used since the first synthetic degradable sutures in poly(glycolic acid) (PGA) were
 3 approved in the 1960s [19]. During the following decades, other products based on polymers of lactic and glycolic acid
 4 were accepted and commercialized as resorbable medical devices. In orthopedics, polyesters are considered a promising
 5 alternative to metallic fixation as their lower mechanical properties prevent stress shielding and offer better load transfer to
 6 the healing bone. They are particularly applied in limb surgeries (anchors, screws and pins), in craniomaxillofacial
 7 osteosynthesis (plates, meshes, screws, cranial flaps, orbital floor) and in spine surgery (cages) [26,139], with a preference
 8 for P(L/D,L)LA (70/30) [25,49,74,140–147]. They can also be used as drug delivery platforms [26]. Bioresorbable
 9 polyesters are very versatile and can show a high variety of physicochemical properties (Table 3). Furthermore, they are
 10 FDA approved for several medical applications, being relatively cost-effective and can be often produced from renewable
 11 sources. Generally, PCL and PGA are then obtained through ring-opening polymerization [26], while PLA on the other
 12 hand can be synthesized via different polymerization processes [46], including poly-condensation, azeotropic dehydration,
 13 enzymatic polymerization (all from lactic acid) and ring opening polymerization (from lactide, cyclic dimer of lactic acid).
 14 Monomers are usually extracted from renewable sources (sugarcane, corn starch), except for ϵ -caprolactone monomer,
 15 which has fossil origin [46,148,149].

16 The degradation of polyesters in vivo occurs primarily through hydrolysis of the ester bonds, although the occurrence of
 17 minor enzymatic degradation by esterase and microbial biodegradation has been also reported [150]. Hydrolysis occurs by
 18 the action of body fluids and it is at the core of the bioresorbability of these polymers. The degradation byproducts can
 19 seamlessly enter physiological pathways and be disposed of through the tricarboxylic acid cycle (TCA) [45,151]. The
 20 hydrolysis rate depends on the size, shape, architecture and crystallinity of the device, but it also depends on the conditions
 21 of synthesis, storage, sterilization and implant location (e.g. vascularization, local pH) [26,45,98,152,153]. The by-products
 22 of this degradation are acidic and can cause a local pH decrease, which leads autocatalysis. Indeed this local acidification of
 23 the medium is a major concern for the use of polyesters [26,100,101,152,154,155].

24 **Table 3:** Thermal, degradation and mechanical properties of the most commonly used polyesters in biomedical devices

Polymer	Thermal		Degradation <i>In vivo</i> rate (months)	Mechanical								Ref.
	Melting point (°C)	T_g (°C)		Tensile			Flexural		Compressive		Shear	
				ϵ_{max} (%)	E (GPa)	σ_{max} (MPa)	E_F (GPa)	σ_{max} (MPa)	E (GPa)	σ_{max} (MPa)	τ_{max} (MPa)	
PGA	210 - 230	35 - 40	6 - 12	15 - 20	7	60 - 100	7	200 - 370	-	-	-	[26,27,46,156]
PLLA	173 - 180	60 - 65	> 24	5 - 10	1.3 - 7	16 - 150	3 - 6	110 - 230	4.8	120	130	[24–30,46,153,157]
PDLLA	Amorphous	55 - 60	12 - 16	3 - 10	1.0 - 3.5	25 - 45	1.9	90	-	-	-	[26,27,46,153]
P(L/D,L) LA (70/30)	Amorphous	55 - 60	-	5	2 - 3	60 - 70	3	130	2 - 3	70-90	45	[25,74,96,140,158]
PCL	58 - 63	-60	> 24	300 - 500	0.3 - 0.4	20 - 40	0.4	-	-	-	-	[26,94][46]
PLGA	Amorphous	45 - 55	1 - 6	3 - 10	1.4 - 7	40 - 70	2 - 3	65 - 125	3 - 4	90-110	-	[25–27,46,73]
PLCL	Amorphous	20	-	-	0.1 - 1.1	5 - 50	-	-	3	90	-	[27,94,95,97]

1 Results have shown that the phenomenon is mass-dependent and as a consequence the use of bioresorbable polyesters is
2 limited in terms of massive (large) devices [42]. Fortunately, small size devices (< 250 μm) usually undergo solely surface
3 degradation and autocatalytic effects do not normally occur. Polyester-based devices are considered generally
4 biocompatible and bioresorbable. Hydrolytic inflammation is reported. This effect is, however, relatively sparse (less than
5 10% cases) and it is concentrated around implantation in scarcely vascularized implant sites (e.g. cartilage) [44,46]. A
6 second form of degradation is thermal degradation, occurring primarily during processing (e.g. extrusion) as a function of
7 temperature and time [159,160]. Above 200°C, polyesters can suffer from depolymerization, pyrolytic elimination, radical
8 or non-radical degradation and transesterification. The melt flow index increases while its MW, viscosity and mechanical
9 properties decrease, sometimes dramatically [153,159–166]. Contributing factors are high shear stresses [30,140,141],
10 presence of oxygen [159] and residual catalyzers (e.g. stannous octanoate) [166]. Finally, degradation can also occur due to
11 sterilization. In particular, if gamma irradiation sterilization (dose > 35 kGy) is used, chain breaking can occur. Protocols
12 are available to optimize sterilization while minimizing degradation [74,143,167,168]. Alternatively, ethylene oxide (EtO)
13 sterilization is a viable alternative to avoid the issue [144]. Challenges and opportunities of these materials are summarized
14 in Figure 4 **Error! Reference source not found.**



15

16

Figure 4: Advantages and drawbacks of bioresorbable polyesters for biomedical applications

1 **4. Regeneration: combining polyesters and bioactive glasses to fabricate tissue engineering scaffolds**

2 A scaffold, as commonly defined in tissue engineering, is a three-dimensional porous construct specifically designed to
3 support and improve the growth of cells seeded on it. Differently from standard implantation techniques, the Tissue
4 Engineering/Regenerative Medicine (TERM) approach is based on the concept of a biodegradable scaffold, made of a
5 combination of biomaterials, biological agents (e.g. growth factors) and, possibly, cells that should promote the
6 development of new tissue and degrade at the same rate of tissue regrowth in order to leave, after a certain time, a
7 completely regenerated tissue with no residual foreign material inside the patient. In the last decades bioresorbable
8 polyesters and bioactive glasses have been both tested as suitable biomaterials in the development of scaffolds targeting
9 various tissues. The explored techniques follow mainly two trends: the first one comprises polymer-based systems with
10 addition of bioactive glass (usually as particulate or fiber); the second one includes glass scaffolds covered/modified with
11 biodegradable polymers by various strategies [14,57,169].

12 **4.1 Polymer-based scaffolds**

13 Embedding bioactive glasses into polyester matrices via the composite fabrication approach [58] can be achieved by a
14 variety of techniques, including traditional scaffold fabrication methods such as solvent casting, particle leaching and
15 Thermally Induced Phase Separation (TIPS) and modern scaffold fabrication techniques, namely additive manufacturing
16 and electrospinning.

17 *4.1.1 Solvent Casting*

18 Solvent casting (SC) of composite scaffolds is a technique that consists of dissolution of the polymer in a compatible
19 organic solvent, mixing of the bioactive glass particle phase (i.e. filler), subsequent casting of the solution in a desired 3D
20 mold and solvent evaporation. SC is an easy and relatively cost-effective technique (since it does not require any major
21 equipment), but has the disadvantage of using solvents that can denature biologically active species added to the polymer
22 and could also remain trapped within the polymer matrix and cause toxicity. Composite scaffolds have been produced by
23 mixing bioactive glass particles with polylactic acid [170]. The composition of the glass, the one of the polymer and the
24 solvent can vary. For instance, various percentages of D and L enantiomers of lactic acid [128,171–174], PLGA
25 copolymers [61,175] and PCL [176,177] have been dissolved in several solvents, such as chloroform [173,174],
26 dichloromethane (DCM) [61], dioxane [128], tetrahydrofuran (THF) [178] and dimethyl carbonate (DMC) [172]. The
27 tested bioactive fillers were 45S5 [61,172–175], 58S [173] bioactive glasses and other customized compositions [128,171].
28 SC can be coupled with Particulate Leaching (PL) in order to develop porosity in the construct [176]. The procedure is the
29 same used for solvent casting, exception made for the addition of a porogen (usually particles of a salt that is insoluble in
30 the chosen solvent) during mixing. After the evaporation of the solvent, the scaffold is placed in a water bath, allowing the
31 salt to dissolve and to leave a porous structure (Figure 5). SC/PL is a highly studied traditional technique to produce porous
32 scaffolds, however the porosity cannot be finely tuned and it is hard to obtain high interconnectivity between the pores
33 [128,169], which is of major importance for fluid penetration as well as cell and tissue growth. One of the largest
34 drawbacks of this technique and is that it is difficult to control the outer shape of the scaffold. Only simple shapes can be
35 made which would have to be potentially be reshaped after fabrication, for example in the surgical theater.

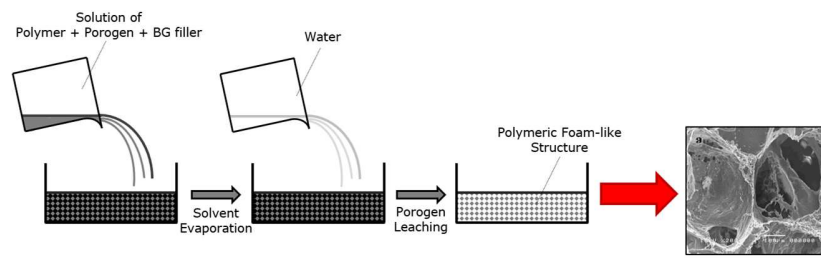


Figure 5: Schematic representation of the solvent casting method to produce polymer/BG composites. SEM image modified from reference [168] with permission of John Wiley & Sons.

4.1.2 Thermally Induced Phase Separation/Freeze Drying (TIPS/FD)

Techniques that overcome the limitations of traditional ways of processing porous composite scaffolds are TIPS and freeze-drying (FD). However, in the case of polyesters, TIPS has the downside of using considerable quantities of solvents [179]. In a typical procedure for composite scaffold production, a mixture of dissolved polymer and inorganic filler is quenched at a temperature below the limit of solubility of the polymer in the solvent. Consequently, the polymer and the particles are forced to fit into the interstitial spaces in between the solidified solvent. When freeze-drying the solidified mixture, the solvent sublimates and what remains is a highly porous composite scaffold usually characterized by strong anisotropy and extensive interconnectivity of the pores (Figure 6). A small quantity of a third non-miscible specie (such as hexane) can be added to the mixture to improve the liquid-liquid phase separation at low temperatures [180]. TIPS/FD allows the fabrication of a number of different 3D topographies since the final features of the scaffold highly vary depending on the final thermodynamic state of the polymer solution and the heat transfer during the process. These phenomena can be controlled by accurate choice of polymer, solvent, ratio between solvent and polymer, freezing kinetics/temperature and freeze-drying parameters. Extensive research has been carried out in order to characterize TIPS/FD fabricated scaffolds combining PLA and various formulations of bioactive glass. Various amorphous copolymers based on mixtures of L- and D- enantiomers have been proven to be interesting candidates for bone tissue engineering applications since the preparation method allows the fabrication of well-tailored tubular pores that can mimic the bone structure. For instance, amorphous P(D,L)LA [13,131,135,181,182], usually dissolved in dimethyl carbonate (DMC), as well as semi-crystalline PLLA [129,132,133,183], usually dissolved in dioxane, have been considered. PCL can be also used [184]. The possibility of producing TIPS P(D,L)LA scaffolds coated with 45S5 BG has been reported [59]. An effective application of the techniques presented so far was recently reported by Kim *et al.* [128] who combined SC/PL and TIPS/FD with a nanofibrous bioactive glass filler produced by electrospinning of a sol-gel precursor. The fibers were mixed together with a polymeric solution and NaCl particles and then, after sublimation of the solvent by freeze-drying, the porogen was washed away. The scaffold showed highly interconnected porosity (~83.6%) and complex hierarchical topography, a feature that, as already discussed, is known to help cell proliferation and migration [178]. Similarly to SC, TIPS/FD does not allow control on the overall shape of the device, meaning that only very simple shapes can be prepared.

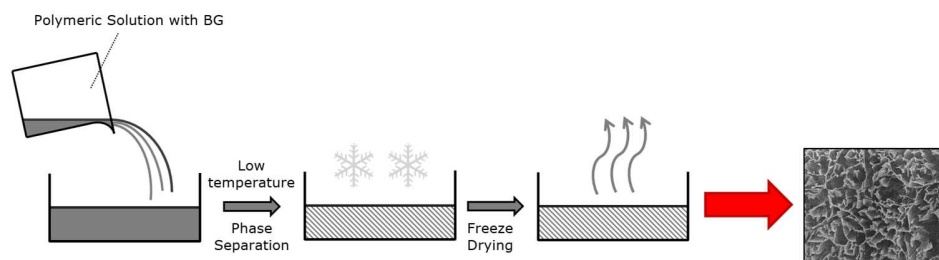


Figure 6: Schematic representation of TIPS/FD suitable to fabricate polymer/BG composites. SEM image modified from reference [174] with permission of John Wiley & Sons.

4.1.3 Microspheres Sintering

Three-dimensional polylactide-based scaffolds with high pore-interconnectivity [185] can be produced from polymeric microspheres, usually made of PLGA, via a technique that mimics ceramic sintering. Briefly, the microspheres are sifted to control the desired size range, then poured in a 3D mold, usually a cylinder, and finally heated slightly above the glass transition temperature of the polymer (i.e. 60-70°C for PLGA) without applying pressure (Figure 7). The polymeric microspheres necessary for this fabrication procedure can be produced using various techniques such as emulsification methods [185–187] and ultrasonic aided polymer spraying [188,189] among others. At this fabrication stage, bioactive glass microparticles of controlled size are added by simple mixing.

Normally, based on reported literature [189], the size of the bioactive microparticles is roughly a tenth of the microspheres size. Moreover, during the production of microspheres, molecules of interest can be added to the polymer, giving the scaffold more chemical and biological features that can enhance the stimulation of cells in the final device. This last point makes microsphere sintering a very versatile technique to create finely tuned drug delivery systems within the scaffold. However, on the downside, it is a fabrication technique that does not allow a fine control over the final structural features of the scaffold and, moreover, polymeric sintered 3D constructs have a relatively low porosity compared to other techniques such as TIPS [190]. A variation on this technique uses subcritical CO₂ and high pressure (i.e. 15 bar) as alternative sintering process [189,191]. This new approach allows the processing of scaffolds at room temperature (i.e. 25°C) so that molecules that would be denatured or inactivated at standard sintering temperatures can be loaded in the polymer.

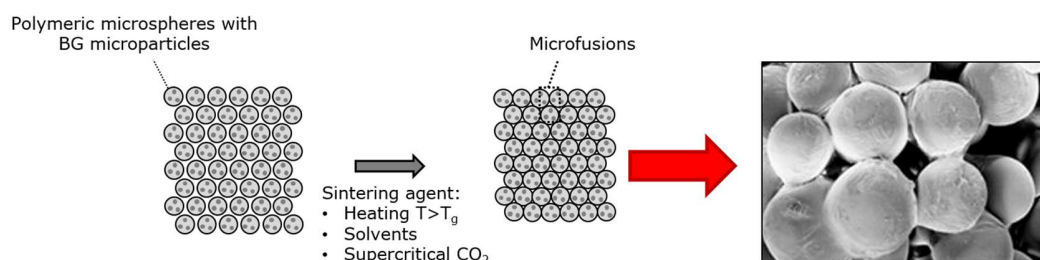


Figure 7: Schematic representation of microsphere sintering. Bioactive glass particles can be added inside the polymeric micro-spheres. SEM image modified from reference [181] with permission of Elsevier.

4.1.4 Additive Manufacturing

The term Additive Manufacturing (AM), also known as Rapid Prototyping (RP) or Solid Free-form Fabrication (SFF) represents a family of techniques that have in common the precise recreation of 3D constructs from a previously developed computer aided design (CAD) by means of layer-by-layer deposition of the desired polymer (Figure 8). AM has been used to fabricate scaffolds and it is attracting considerable interest because of its ability of creating completely interconnected porous scaffolds that can achieve a more accurate structure for specific applications. Furthermore, with AM, devices can be fabricated with theoretically any shape, even the most complex. Scaffolds and implants could even be designed *ad hoc* for each patient. Investigations of polyester composites as materials for rapid prototyping are rapidly becoming an expanding field, with more studies published every year [192–196]. Although generally very promising in terms of reproducibility and scalability, processing by FDM (Figure 8) can be challenging, requiring high printing temperature or the use of additives [195]. Serra *et al.* [194] reported a possible solution to overcome this limitation via the printing of a blend of P(L/D,L)LA (5/95) and CaP glass into porous layered structures. Polyethylene glycol (PEG) was added to the mixture as plasticizer to facilitate the processing of the scaffold [197].

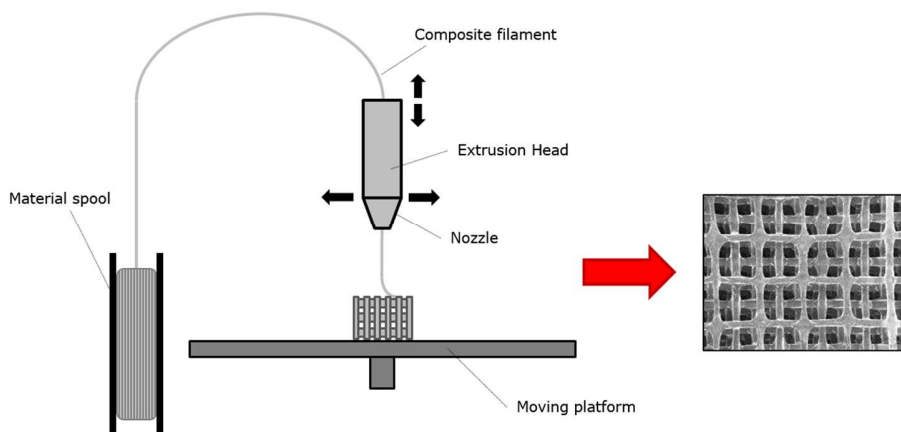


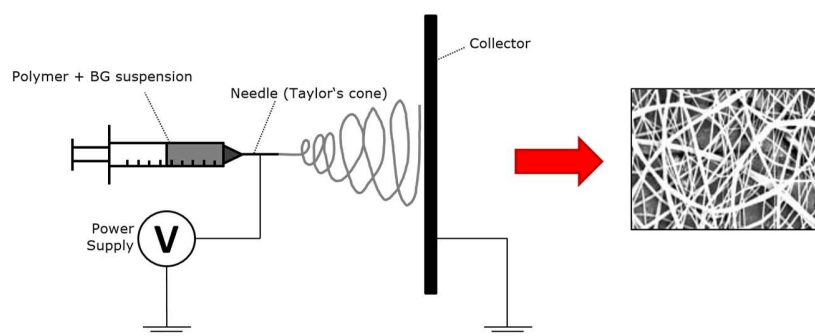
Figure 8: Schematic representation of fused deposition modelling (FDM). SEM image modified from reference [186] with permission of Elsevier.

Other alternative SFF approaches are also currently under investigation. For instance, Kolan *et al.* [198] obtained remarkable results printing a slurry of PCL and bioactive borate glass in chloroform. The PCL/BG scaffold structure was then used to embed a Pluronic F127 hydrogel used as cell suspension medium (dual printing). Scaffolds produced with this technique show promising degradation behavior coupled with the formation of a hydroxyapatite-like layer on the surface, as confirmed by a similar study by Zehnder *et al.* [197].

4.1.5 Electrospinning

Electrospinning is a very versatile process to produce sub-micrometrical and nanosized fibers with a significantly smaller diameter compared to traditional fiber fabrication techniques. The fibers are collected to form an interconnected web in order to produce fiber mats that serve as tissue engineering scaffolds, targeting the regeneration of skin, blood vessels, nerves and osteochondral defects [199,200]. The principle of electrospinning is to overcome the surface tension of a droplet

1 at the tip of a millimeter sized needle by applying a high-voltage electric field (around 10-20 kV) between the needle itself
2 and a collecting plate in front of it (Figure 9). Increasing the electric field deforms the droplet into a so-called Taylor cone
3 and forms a polymer jet diffusing from the needle. The solvent evaporates from the jet, which elongates and becomes
4 thinner. This process occurs several times in rapid succession leading to a large number of electrically charged fibers
5 moving toward the collector. Many parameters influence the characteristics of the fabricated fibers, among them the most
6 relevant are the properties of the solution (i.e. viscosity, elasticity, conductivity, and surface tension), the processing
7 variables (i.e. the applied voltage, the flow rate of the solution or the needle tip-collector distance) and the ambient
8 parameters (temperature, humidity, air flow in the electrospinning chamber) [199]. Varying these parameters it is possible
9 to tailor specific complex topographies, such as porous [201] or hollow [202] fibers.



10

11 **Figure 9:** Schematic representation of electrospinning of polymer/BG composite fibers. SEM image modified from reference [198] under
12 Creative Commons license.

13 A bioactive particulate phase can be added to the polymer solution to prepare micro- or nanocomposite scaffolds with
14 enhanced properties, as comprehensively discussed in a very recent review [203]. This approach has been applied to
15 fabricate electrospun polylactic acid with embedded bioactive glass nanoparticles [204,205]. Similarly, BG/PCL fibers can
16 be also produced [206–208]. Typically, concentrations of bioactive glass particles in the range 5-40 wt. % of the polymer
17 are mixed in the polymeric solution and then the suspension is electrospun. In a recent relevant publication, PLLA
18 embedding bioactive silica-based glass particles (SBA2) was electrospun and a uniform dispersion of bioactive glass
19 powder within the polymer fibers was obtained. Compared to neat PLLA fibers, the composite is characterized by
20 significantly higher elastic modulus, promoted HCA deposition thanks to the BG, better pH control and therapeutic ion
21 release. These promising results make this system very appealing as a multifunctional system for both bone and soft tissue
22 engineering applications [209], especially when coupled with the use of benign solvents (e.g. acetic acid, acetone) by so-
23 called green electrospinning [210].

24 An alternative strategy to the spun composite approach is proposed by Sachot *et al.* [202,211], who created a complex
25 hierarchical topography on the surface of P(D,L)LA electrospun fibers by covalent coupling between the polymer and
26 organically-modified bioactive glass (ormoglass) particles. Ormoglass is produced via an alkoxide sol-gel method followed
27 by partial hydrolysis, in this way a glass network with the presence of ethyl and other organic groups is obtained [212].
28 Results showed that the Ormoglass surface treatment improved the hydrophilicity and mechanical properties of the original
29 polymer electrospun fibers [202].

1 Electrospinning has also been applied to melts. Initially, melt electrospinning was developed to reduce the concerns
2 associated with the use of solvents. However, this technique quickly gained more resonance as it started to be coupled with
3 an additive manufacturing approach that aimed not only at the fabrication of microfibers, but also to finely control their
4 deposition to fabricate complex 3D structures [213]. Over the last decade Melt Electro-Writing (MEW) has emerged as a
5 very promising AM technique for a few selected niches, mainly filtration, soft matter applications and TERM scaffolds
6 [214]. MEW applies the same principle of electrospinning, but uses applied voltage in a different manner: while in
7 electrospinning high voltage is used to create electrical instabilities (i.e. “whipping” [213]) leading to the formation of thin
8 fibers, electrowriting uses lower voltages that allow for continuous and controlled fluid deposition at low flow rates.
9 Depending on the configuration and fluid properties, the flow rate can be extremely low and whipping free, while
10 permitting the formation of sub-micrometric fibers. In other words, submicrometric fibers are obtained in one case
11 (electrospinning) by high voltage whipping, while in the other by careful tuning and sustaining of a stable low flow rate
12 using lower applied voltage [213]. Two reviews discussing the recent advancements in MEW, the most promising results
13 obtained to date, and the challenges connected to the use of this technique are available [214,215]. In the context of
14 polyester/BG composites, a blend of PLA and a PLA-PEG-PLA block polymer together with 45S5 microparticles was used
15 for the MEW fabrication of composite meshes with various widths, shapes and fiber diameters [216]. PCL composites are
16 also suitable for this technique, as it was recently confirmed with strontium-doped bioactive glass [197].

17 **4.2 Bioactive glass-based scaffolds**

18 *4.2.1 Foam Replica*

19 The foam replica technique was successfully applied to the fabrication of BG scaffolds in 2006 using polyurethane foams
20 as template [217]. Later, also natural marine sponges were studied to make stronger BG scaffolds [90,218]. A typical
21 process starts with the preparation of a BG/binder slurry. The foam templates are soaked in the slurry, dried and slowly
22 burned at high temperatures to remove the polymer of the slurry and the template. Then the green bodies are sintered in
23 order to get final BG scaffolds (Figure 10) [169]. The scaffolds can be then further processed and coated with a polymeric
24 layer. Many polymeric coatings are reported in literature, among them PLA-based coatings [92,130,219–224]. The coating
25 of scaffolds can significantly improve their mechanical properties and, furthermore, the polymer can be engineered and
26 used as a controlled drug delivery carrier for various species. Among others, systems that deliver zoledronic acid (a drug
27 against osteoporosis) [221], vancomycin [220] or antibacterial selenium nanoparticles [219] are reported. The disadvantage
28 of coating BG scaffolds with polymer is that a drop in bioactivity can occur due to the coverage of the BG surface by the
29 relatively inert organic coating [92]. However, avoiding a complete polymer coverage, or achieving infiltration of the
30 polymer into the defects (e.g. microcracks) of the BG struts, results in notable toughening (and strengthening) of the
31 scaffolds [225].

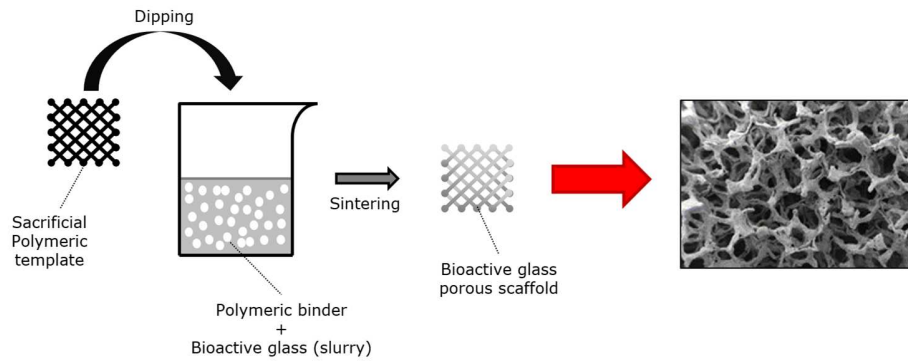


Figure 10: Schematic representation of the foam replica method for the production of bioactive glass scaffolds, according to the protocol introduced by Chen et al. [217]. SEM image modified from reference [209] with permission of Elsevier.

4.2.2 Additive Manufacturing (AM)

As for polymeric materials, AM techniques are being increasingly investigated as feasible methods to produce scaffolds using bioactive glasses as raw materials [197]. The complete control of the pore network topography and interconnectivity is a very appealing characteristic of SFF. Recently, bioactive glass scaffolds, of 45S5, 13-93 and 6P53B (wt. % 52.7 SiO₂, 10.3 Na₂O, 2.8 K₂O, 10.2 MgO, 18.0 CaO, 6 P₂O₅) compositions among others, have been produced via AM processes, especially *robocasting* [10,134,225–230]. Robocasting is an extrusion-based technique generally suitable for dense ceramics and composites [231]. It involves the layer-by-layer deposition of colloidal slurries (inks) and the subsequent burning out of the ink to give a final sintered body. The rheological parameters of the printing ink, such as apparent viscosity, yield stress and dynamic elastic modulus, are crucial in the determination of the final properties of the scaffold. An optimal robocasting ink must flow properly and have excellent shape retention upon deposition. A typical ink for the fabrication of scaffolds from bioactive glass is a water suspension of the desired glass particles and various organic additives to optimize the viscosity of the ink. Among others, additives such as polyethylenimine (PEI) [232,233], poloxamers (e.g. Pluronic F-127) [134,228] or several derivatives of methylcellulose (MC) [225–227,229,232] are reported. Scaffolds produced with this technique still present one of the main disadvantages of bioactive glass scaffolds: excessive brittleness to be used in structural and load-bearing applications [227]. Moreover, the fine control of the architecture of robocasted scaffold is still an issue to be addressed [227]. This is because, after sintering and the removal of the organic part of the ink, robocasted scaffolds tend to shrink: this could be a limiting factor when fabricating complex shapes. BG scaffolds can be combined with polylactic acid, among other polymers, to overcome these limits. Melt infiltration of BG scaffolds with PLA has been reported [225,227]. Briefly, after robocasting and sintering, the scaffolds were immersed in a bath of molten polymer at 227°C. Polymer infiltration improves the mechanical properties of bare scaffolds by mainly two mechanisms: defect healing and stress shielding. When the polymer phase infiltrates in the cracks of the bioactive glass scaffold, it seals them achieving a better distribution of the load. Moreover, toughening mechanisms, particularly crack bridging, can be activated [197]. In addition, the continuous polymeric layer that forms on the surface of the struts provides stress shielding, meaning that it can bear part of the load (especially if a stiff polymer is used) and protect the inner inorganic phase [227].

SCAFFOLD FABRICATION TECHNIQUES

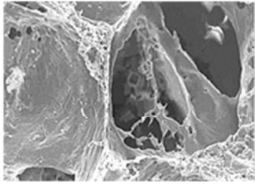
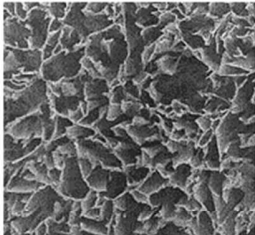
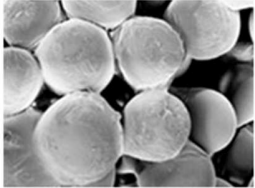
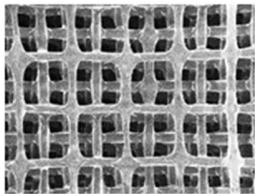
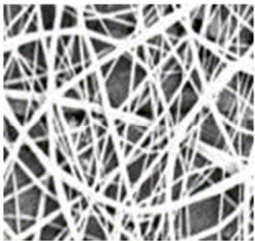
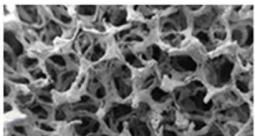
		Advantages	Disadvantages
Solvent casting particulate leaching		<ul style="list-style-type: none"> Simple and cost effective 	<ul style="list-style-type: none"> Use of solvents Only few geometries Closed porosity
Thermally induced phase separation		<ul style="list-style-type: none"> 100% interconnected porosity Control on topography Can be combined with SC/PL Closed porosity 	<ul style="list-style-type: none"> Use of solvents Limited shapes
Microsphere Sintering		<ul style="list-style-type: none"> No solvent or harsh processing conditions Adaptable for composites Drug delivery capability 	<ul style="list-style-type: none"> Lower and scarcely controllable porosity Limited shapes
Additive Manufacturing		<ul style="list-style-type: none"> Total control on shape and porosity 100% interconnectivity Reproducible 	<ul style="list-style-type: none"> Time consuming Limited range of materials Cannot create nanometer-sized features
Electrospinning		<ul style="list-style-type: none"> Extracellular matrix-like nanometric features High interconnectivity For polymers, composites and sol-gel direct spinning 	<ul style="list-style-type: none"> Use of solvents Spinning parameters are hard to optimize Difficult to scale-up Time consuming
Foam Replica		<ul style="list-style-type: none"> High interconnectivity Easy to scale-up 	<ul style="list-style-type: none"> Limited shapes

Figure 11: Summary of the main advantages and drawbacks of the scaffold fabrication techniques

4.3 Properties and Characterization of composite scaffolds

The characterization and property assessment of scaffolds for tissue engineering highly depend on the final targeted tissue as well as the fabrication technique considered (Figure 11). In most cases, scaffolds produced using PLA and bioactive

1 glasses are intended for bone tissue engineering. This is mostly a consequence of the strong positive effect that BGs have
2 on the biomineralization process. In this section, we will discuss the main properties of PLA/BG scaffolds for tissue
3 engineering, particularly focusing on bone regeneration. According to Jones [10], there are six major requirements for bone
4 tissue scaffolds:

5 I – Porosity: ideal scaffold architectures are porous with high interconnectivity that allows fluid and cell infiltration,
6 exchange of metabolites and catabolites, vascularization and bone in-growth;

7 II - Biocompatibility and bioactivity, meaning that the scaffold promotes a healthy bond between host material and bone,
8 stimulating cell attachment and biomineralization;

9 III - Tailored degradation rate;

10 IV - Mechanical properties close to the ones of physiological bone so that the scaffold can bear the load during healing
11 keeping at the same time a proper status of mechanical stimulation in the tissue

12 V - Customized shape and internal structure in order to fit the bone defect of each patient

13 VI - Industrial competitiveness: the scaffold must be relatively easy to sterilize, scale-up and certify as a medical device.

14 Porosity and porous morphology are mainly determined by the fabrication technique, as previously discussed in Sections
15 §4.1 and §4.2. At the same time, the industrial aspects of scaffold development fall outside the aim of this section and
16 similarly do the issue of shape customization, since it is mainly a clinical problem, so they will not be discussed here.

17 4.3.1 Biocompatibility and bioactivity

18 In a case study regarding PLA/BG scaffolds (BG composition $\text{SiO}_2:\text{CaO}:\text{P}_2\text{O}_5 = 55:40:5$ %mol) prepared by TIPS/FD,
19 Hong *et al.* [132] analyzed the biomineralization of nanocomposite scaffolds via SEM and confirmed their qualitative
20 evaluation by EDX, XRD and FTIR. Their results showed the presence of an optimal window of BG concentrations (i.e. 5-
21 20 wt. %) that enhances the formation of cauliflower-like hydroxyapatite crystals. Conversely, it was observed that the
22 development of bone-like apatite on PLLA/BG (30 wt. %) composites is delayed, compared to compositions with less
23 bioactive glass. This result suggests the existence of an overloading point at which an excess of exposed BG on the surface
24 of the scaffolds decreases the development rate of apatite [129,132,234]. A possible explanation for this phenomenon is the
25 occurrence of excessive degradation of the structure for high BG loading, further increased by the high porosity of
26 scaffolds [132]. As a matter of fact, dense PLA/BG composites were characterized by outstanding bioactivity at higher BG
27 content (> 30 wt. %) [98], compared to porous scaffolds, cluing that excessive degradation could play a role in determining
28 the setting of an optimal loading threshold [129,132,234].

29 Usually, as reported by several authors [187,235–238], no stimulation of apatite formation is induced by plain polyesters
30 when immersed in SBF, deeming them non-bioactive materials. Few studies showed that the porous structure of polymeric
31 foams alone could induce minor deposition of HCA, probably due to nucleation triggered by local accumulation of salts in
32 niches of the porous structure [129,131]. However, this effect from completely polymeric foams is scarcely reproducible
33 and the use of bioactive fillers to introduce a steady and robust apatite-formation ability on the biomaterial surfaces should
34 be sought.

4.3.2 Impact on degradation

The core advantage of PLA/BG systems is the combination of the acidic and alkali degradations of the two components seeking to obtain a buffering system that stabilizes the kinetics of both degradations [169,239]. For this reason, it is important to fully characterize the degradation behavior of PLA/BG scaffolds. In vitro acellular degradation tests are easy and routine assays that can be performed using various media, such as PBS [240] or SBF [135,228,241], and then analyzed in terms of pH variation [240], molecular mass variation of the polymer by size exclusion chromatography [135,240], water absorption and weight loss. These tests can help understanding the effect that a BG filler can have on the polymeric matrix. In particular, this effect is highly composition-dependent. For instance, in a study by Barbeck et al. [242], the weight loss of 3D printed P(L/D,L)LA/calcium-phosphate bioactive glass (44.5 P₂O₅ - 44.5 Ca₂O - 6 Na₂O - 5 TiO₂ mol. %) scaffolds was halved after eight weeks in water compared to the polymeric control. On the contrary, when highly reactive BG (e.g. 45S5) is used, the pH can be increased during dissolution, enhancing alkali-based hydrolysis and thus the degradation rate of the polymeric matrix [74]. This effect was reported both for PLA and PCL [74,169,243,244]. Most interestingly, alkali-based hydrolysis reduces the chances of autocatalysis by the polymer: the matrix will then undergo surface degradation instead of bulk degradation, without the risk of cavity formation and, consequently, of catastrophic failure [239].

4.3.4 Mechanical properties

Mechanical testing is particularly interesting when evaluating the contribution of the filler phase to the overall mechanical properties of polymer-based PLA/BG scaffolds [129,135,173,174,181,188,194,227], especially for foam systems. As a matter of fact in some cases the nature of the porous structure determines the mechanical properties of the scaffold significantly more than the addition of bioactive glass to the polymer matrix (compressive modulus ~ 1 MPa), as previously reported [181,245]. On the contrary, other authors showed that the addition of BG to a polyester matrix can significantly increase (two-fold) the mechanical properties of scaffolds produced by microsphere sintering (from 26 to 52 MPa). Since microsphere sintered scaffolds are characterized by relatively low porosity (see §2.1.1.3), the nature of the material has a stronger effect in the determination of the mechanical behavior than pore content. There is a clear trade-off between porosity and mechanical properties and the optimal working area and fabrication technique to get the best out of both has to be determined yet. In any case, the mechanical properties that can be reached with most scaffold fabrication techniques are still significantly lower when porosity exceeds ~80% (Table 4) than the target properties of bone tissue, especially cortical one [246].

Table 4: Examples of mechanical properties of porous scaffolds based on composites of polylactide and Bioglass®

Type of polyester	Ceramic percentage (wt. %)	Porosity (%)	Pore size (µm)	Ultimate strength (MPa)	Modulus (MPa)	References
PLGA	75	43	89	0.42	51	[11,187,247]
PLLA	20 - 50	77 - 80	~100	1.5 - 3.9	137 - 260	[129]
PDLLA	5 - 29	94	~100	0.07 - 0.08	0.62 - 1.2	[131,135,181]

The assessment of the time-dependant mechanical properties as a function of degradation and biomineralization must be carried out [135]. Caridade *et al.* [174] developed a bioresorbable membranous PLA/BG system for guided tissue/bone

1 regeneration (GTR/GBR), a specific therapeutic strategy that was born to overcome the problem of soft tissue cells growing
2 faster than ligament and bone tissues. It consists in using a barrier membrane to confine and protect the defect so that the
3 right tissue can properly regrow [248,249]. In this particular application, the tensile mechanical properties of the chosen
4 material are crucial since the device must stretch and follow the morphology of the defect. Results suggest the BG fillers
5 reduce the effect that temperature has on the glass transition of the polymer and, ultimately, on the construct stiffness. The
6 group also evaluated the changes in mechanical behavior between dry and wet state, concluding that there are significant
7 differences and that wet-state mechanical testing results are closer to the actual behavior of the device in real clinical
8 conditions. Finally, another reported approach for the evaluation of the mechanical properties of PLA/BG scaffold consists
9 in the assessment of the surface local mechanical properties via Atomic Force Microscopy (AFM) [202]. This technique
10 offers increased detail in terms of mechanical properties at the micro- and nanoscale, compared to standard macroscopic
11 testing. In a case study by Sachot *et al.*, for instance, AFM was successfully used to characterize the flexibility, continuity
12 and delamination of PLA/glass coatings with high resolution, concluding that the composite approach was effective in
13 increasing the mechanical properties of the native polymer without disrupting the continuity and flexibility of the coating
14 [202,250].

15 **4.4 *In vitro* and *in vivo* biological testing**

16 A substantial amount of *in vitro* reports on the biological properties of bioactive glasses and composites is available in
17 literature [13,61,74,92,128,131,170,172,175,182,185,187–189,194,202,204,219,223,251–253]. The assessment of the
18 cytocompatibility of newly designed scaffolds is a key feature in the development of new technologies for tissue
19 engineering applications. The cultured cell strains are multiple. The most common cells considered to test BG and
20 polyester/BG composites are osteoblasts [131,185,187,204,252,253] and mesenchymal stem cells (MSCs)
21 [128,185,194,251]. The response of cells to the material after desired time-points of culture can be assessed using
22 numerous techniques such as morphology observations [182,253], colorimetric assays [13,92,174,182], fluorescence
23 staining [136,172] and quantification of specific markers of cell activity (e.g. alkaline phosphatase (ALP), collagen)
24 [128,187]. The typical protocol approach consists in performing both quantitative and qualitative tests, in order to get
25 complete information regarding the condition of the cells, both in terms of how metabolically active cells are and how is
26 their phenotype [194]. In a case study, Haimi *et al.* [254] studied the effect of the addition of BG (5 Na₂O, 7.5 K₂O, 3 MgO,
27 25 CaO and 59.5 SiO₂, mol. %) on the proliferation and differentiation of adipose stem cells (ASCs) cultured on PLA-
28 based freeze-dried composite scaffolds: no relevant difference in cell viability and proliferation was assessed, while filler
29 addition significantly increased the expression of ALP, probably due to the release of ions (silicon and calcium in
30 particular) from the glass. The properties of solvent cast PCL films were also studied depending on the composition and
31 amount of filler added. The presence of the bioactive glass filler was linked to optimal osteoblast attachment and
32 proliferation, as well as stimulating cell differentiation, osteoinduction and matrix mineralization [244]. Furthermore, both
33 bioactivity and osteoinductivity could be finely tailored by the use of a different glass composition, in particular by varying
34 the amount of calcium and phosphate precursors during synthesis [244].

35 A few PLA/BG technologies for scaffold were also validated using *in vivo* models, usually in rat [57,134,251], so that the
36 actual behavior in an organism, particularly regarding bioactivity and risks of oncogenicity, could be assessed. In a relevant
37 study, mesenchymal stem cells and endothelial progenitor cells were isolated from rats, seeded into PLA/BG scaffolds and

1 implanted in critical size skull defects of 6 mm of diameter for 3 months. After this period, the animals were put down and
2 samples of blood, plasma and vital organs were collected. The organs were then prepared for immuno-histological
3 examination. Relevant findings of the study include the confirmation of the safety of PLA/BG scaffolds in terms of
4 toxicology, limited inflammation and lack of oncogenicity. Moreover, the authors reported a higher degradation rate not
5 only when compared to *in vitro* studies, but also to *in vivo* studies on PLA without bioactive glass. *In vivo* testing on porous
6 PLA-based composite scaffolds was also performed with previous seeding of bone marrow mesenchymal stem cells inside
7 the construct, with highly improved results compared to a cell-less control. Similarly, the beneficial role of growth factor
8 release (e.g. bone morphogenic proteins, BMPs) from scaffolds was also evaluated in a rabbit radial bone model with
9 remarkable results in terms of the formation of new bone with sufficient strength and satisfactory anatomical structure
10 [255]. In spite of the relevant results, *in vivo* testing has significant disadvantages: observation periods are limited and the
11 results usually are characterized by high standard variations and are hard to interpret [256]. The actual benefit of *in vivo*
12 studies became a hot topic among the scientific community, in particular the question is open regarding what are the most
13 promising materials that should be tested *in vivo*. These concerns determine general wariness when using *in vivo* models.
14 Future research on scaffolds will need to move in the direction of reduction of the extent of animal testing (3Rs principle)
15 as well as on the design and optimization of existing and new alternative models, such as the use of complex bioreactors
16 [257].

17 **5. Repair: combining polyesters and bioactive glasses in molded implants**

18 In parallel to their use for the fabrication of TERM scaffolds, polyester/BG composites can be also molded into shape to
19 produce bulk (dense) implants for orthopedics and craniomaxillofacial surgery. Molded implants are constructs
20 manufactured into functional shapes through thermomechanical treatments. These treatments include compression,
21 injection and extrusion. In addition, the thermoforming process is often preceded by a blending of the inorganic and organic
22 phase through either solvent casting or traditional compounding, as detailed in the next section.

23 **5.1 Synthesis and manufacturing of granules**

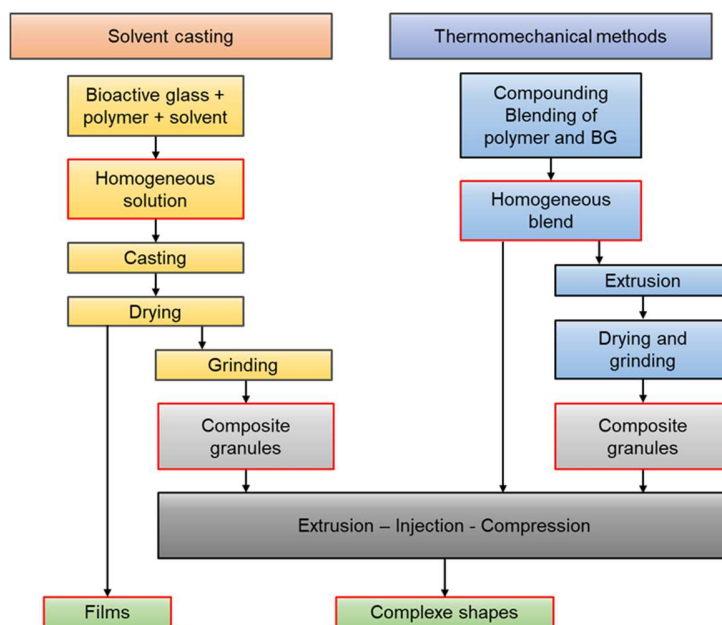
24 Before their processing into implants, composites are fabricated into granules or pellets that aid the process and help
25 standardization. There are mainly two strategies for granules fabrication: solvent casting-aided or direct blending
26 thermoplastic manufacturing (Figure 12).

27 *5.1.1 Solvent casting method*

28 Solvent casting (SC) consists of dissolving a polymer in an adequate organic solvent, mixing with the BG particle phase
29 (i.e. filler), casting of the solution and evaporating the solvent evaporation. To prepare films the solution is preferably cast
30 onto plates [30,93,94,157] while precipitation in water would yield composite granules [74,158,258]. After evaporation, the
31 composites can be further processed (e.g. milling) to obtain a homogeneous product. Previous studies have shown the
32 possible use of SC granules for compression molding of plates, dumbbells or films [30,83,85,93,157,158] as well as
33 injection of 3D shapes such as cylinders or interference screws [74,141,259]. The SC method is interesting because the
34 protocol is simple and it does not involve investment in bulky and expensive equipment (e.g. extrusion equipment).
35 Moreover, this method minimizes material loss and avoids high temperature, thus reducing the thermal degradation of

1 polyesters. Although practical and cost-effective, SC requires the use of large quantities of toxic solvents (usually
 2 chloroform) that may remain in the final product, harm the patient as well as the operator and also contribute to overall
 3 environmental pollution. A possible solution to this issue is the use of less toxic solvents such as acetone. Nevertheless,
 4 residual solvent are known to act as plasticizer and alter the mechanical properties of the final material [28,158,260,261].
 5 For instance, Rhim *et al.* [28] showed that a PLA films with 13 wt. % residual chloroform films showed remarkably higher
 6 ductility, 40% decrease in glass-transition temperature and 60% decrease in tensile strength compared to direct thermo-
 7 compressed ones processed at 190°C. In addition to solvent concerns, this technique also has limitations in terms of filler
 8 dispersion homogeneity: the polymer concentration has to be carefully tailored. Low concentration leads to sedimentation
 9 during drying [262], while high values impede filler dispersion [1].

10



11

12 **Figure 12:** Flowchart summarizing the main steps occurring when processing composite granules for molded implants using a solvent
 13 casting-aided thermoplastic manufacturing (left) or a direct blending method (right).

14 **5.1.2 Thermomechanical method**

15 Thermomechanical manufacturing (TMM) avoids solvents and allows the direct fabrication of composite manufactured
 16 pieces or pellets. The polyester pellets and the BG powder are initially blended to obtain a homogeneous feeding mixture
 17 [1]. Possible strategies include melt blending in a batch mixer at ~100°C (i.e. compounding) [60,263], roller mixing at RT
 18 [73] or cryogenic blending (to avoid hydrolysis) [96]. Then, the mixture is either directly extruded, injected or compressed
 19 [60,140,142,263,264] or mixed again before its final processing [73,96,239]. TMM parameters can vary greatly in function
 20 of the composition of the material: PCL is processed around 80°C, while with PLA and PLGA temperature range between
 21 150°C and 200°C. The process is normally carried out in air, but the use of nitrogen is also reported [96].

22 This process involves a more considerable use of high temperatures, pressure and shearing stress that can be detrimental to
 23 the polymer as compared to the SC method. Thermal and hydrolytic degradation can highly impact the final properties of

1 the material, especially in presence of water [265], high pH (due to BG) [96] or high shear stress [30,140,141]. Careful
2 understanding and tailoring of processing parameters is key. Dergham [140], for instance, highlighted how an apparently
3 small change such as the choice between co-rotating and contra-rotating twin screw extrusion (TSE) can have drastic
4 consequence on the MW of the polymer in the final composite. P(L/D,L)LA (70/30) and 45S5-P(L/D,L)LA (70/30) were
5 extruded in both modes at two speeds (20 rpm and 30 rpm). Due to the higher shear stress values in contra-rotating TSE, a
6 more significant drop in MW was measured compared to the co-rotating one. Interestingly, 30 rpm performed better than
7 20 rpm: the difference in shear stress caused by the higher rotation speed is less important than its contribution to reduce
8 the exposure time to high temperatures in the extruder.

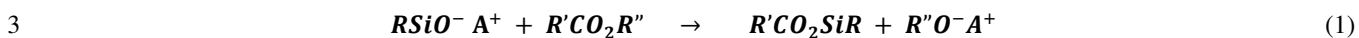
9 Unlike polyethylene [266], polyesters also showed sensitivity to BG, especially at high temperature [94,96,141] and with
10 highly reactive BG [158]. Manufacturing polyester/BG composites poses significant degradation risks for the polymer.
11 Several studies [85,96][158] reported that the color of a BG-P(D,L)LA composite can turn amber when exposed to high
12 temperature depending on the composition and the content of the BG. This suggest that different chemical modifications of
13 the polymer might occurred during TMM. Generally, higher BG ratio and lower particle size decrease the glass transition
14 and decomposition temperatures of the polyesters after processing [30,94,158]. Although the PCL, PLLA and PLCL
15 polymers have good thermal stability and can be easily thermo-manufactured, the incorporation of BGs, and 45S5 in
16 particular, can reduce their thermal stability, resulting in a drastic decrease of MW. This phenomenon is more critical for
17 PLLA since its ester linkage density is higher and more likely to react. Understanding the degradation behavior, the nature
18 of the degradation by-products of the material and the interactions between BG and polyesters is essential when using this
19 kind of processes, especially when the final product is intended for use in a biomedical application. Thus, it appears that a
20 liquid on solid chemical reaction occurs when mixing BG with polyester, regardless of the method of fabrication. The
21 following section is dealing with the physical and chemical nature of these interactions between the two phases of the
22 composite.

23 **5.2 Filler/matrix interface interactions**

24 *5.2.1 Chemical interactions*

25 Vergnol et al. [74] showed that the process of 45S5-P(L/D,L)LA (70/30) granules through SC with water precipitation
26 induced a degradation of 52% of the molar mass of the polymer matrix. A subsequent injection molding step provoked a
27 drop of 75% of the molar mass of the composite while the neat polymer only dropped by 65%. The precipitation in water
28 probably causes the premature dissolution of BG, which then releases species that alkalinize the medium [267] and
29 catalyzes the hydrolysis of the polymer [268]. Prior to dissolution, BG can also adsorb water [269], increasing once again
30 hydrolysis especially when pH and temperature are high [98,160]. Excluding degradation due to radiation-mediated
31 sterilization (see § 3.2.3), the TMM stage is the processing step that is known to causes the highest rate of degradation
32 [73,74]. Fourier transform infrared spectroscopy (FTIR) measurements showed that the initial incorporation of the 45S5
33 BG into a polyester matrix causes an increase in the relative intensity of the band attributed to carbonyl stretching (1600
34 cm^{-1}), especially when the polymer is cast into water [158]. This band tends to increase after TMM [96,140,141]. Several
35 studies also showed that decreasing the BG particle size can increase the degradation phenomena due to higher surface area
36 and degradation rate [60,140,158]. The proposed explanation for this phenomenon is that the thermal processing catalyzes a

1 degradative reaction between SiO^- and ester moieties into carboxylate salts and oligomeric fragments [94,96] or into esters
2 [141]:



4 The glass composition also has strong impact on the final molecular weight of the matrix polymer. Varila *et al.* [85]
5 reported the different interactions that 45S5, S53P4 and S68 BG (45-90 μm particle size) have with P(L/D,L)LA (70/30).
6 The molecular weight of P(L/D,L)LA (70/30) decreased from 200 kDa to respectively 42 kDa, 44 kDa and 160 kDa after
7 being subject to hot-compression processing at 200°C in presence of 50 wt. % 45S5, S53P4 and S68 BGs, respectively. A
8 significant color change was observed depending on the formulation used. 45S5-P(L/D,L)LA (70/30) and S53P4-
9 P(L/D,L)LA (70/30) composites are amber whereas the S68-based composite remains white with only an increase in
10 opalescence. The interface between the two phases is probably affected by the reactivity of the specific BG considered. In
11 the presence of moisture, highly reactive BGs can adsorb water and start dissolving. In humid atmosphere, depending on
12 the granulometry, the water uptake of highly reactive BG could reach more than 100 wt. %, leading to the formation of new
13 crystalline species and particle cracking after drying [158]. This in turn catalyzes polyester hydrolysis. Glasses with higher
14 network connectivity such as S53P4 (NC = 2.54) have lower reactivity and dissolution rate, compared for instance to 45S5
15 (NC = 2.12), and as a consequence degrade less the polymer at the interface. In addition to that, S68 is a glass with low
16 sodium content (13 mol. % compared to 23 and 24 mol. in S53P4 and 45S5, respectively). Since sodium is a species added
17 to a glass to increase its reactivity and dissolution rate [270], a decrease in its content could result in a more stable glass that
18 shows less detrimental effects towards the surrounding polymeric matrix. These observations were further corroborated in
19 another study underlining that the increase in phosphate content can also enhance BG reactivity, leading to higher
20 degradation rates [158]. Scanning Electronic Microscope (SEM) confirmed this hypothesis, showing that S68 BG
21 composite are characterized by clearly superior interface properties (i.e. absence of cavities around BG particles) compared
22 to 45S5 and S53P4 composite samples. In other words, the properties of the interface are likely to control the degree of
23 embrittlement of the composites and bioactive glass particles with a poor interface with the polymer may be considered as
24 defects.

25 5.2.2 Physical interactions

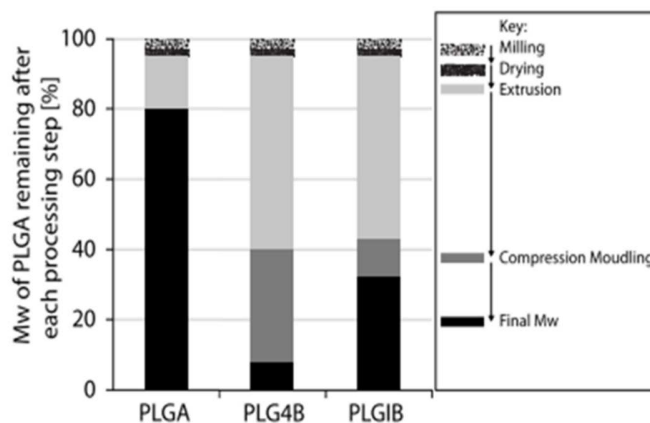
26 In addition to the chemical modifications, incorporating BG within the polymer matrix generates defects that are
27 proportional to the particle size. Macroparticles (>300 μm), in particular, can create large defects that have a significant
28 effect on the overall mechanical properties of the material [140] and reduce the applicability of the composite for small
29 devices. Many studies reported poor interface properties and/or voids between particles and matrix
30 [73,85,96,140,141,158,168]. In general, adding BG particles induced a decrease in the mechanical strength (compression,
31 traction, flexion) coupled with an increase in stiffness compared their respective polymeric control [25,73,74,140,157,158].
32 For instance, when mixing P(L/D,L)LA (70/30) with 30 wt. % and 50 wt. % 45S5 BG microparticles ($D_{50} = 3.5 \mu\text{m}$) the
33 compressive modulus increased from 2.3 GPa (neat polymer) to 2.6 GPa and 2.7 GPa, respectively. In parallel, the
34 compressive strength decreases from 80 MPa to 70 MPa and 60 MPa, respectively [140]. Similarly, Niemela *et al.* [25]
35 showed that adding 20 wt. % of 13-93 bioactive glass in self-reinforced P(L/D,L)LA (70/30) matrix results in an increase
36 from 2.9 to 3.3 GPa of the bending modulus together with a decrease in bending strength from 127 to 108 MPa. Defect-

1 dependent variations in mechanical properties are linked to other important parameters, primarily the morphology and
 2 composition of the glass. The shape of the particles can affect several aspects of processing. Angular particles are more
 3 likely to cause stress concentrations and thus poor mechanical properties and high shear stress during TMM, while
 4 spherical particles have worse filler/matrix interlocking due to their smoothness [1,73]. In a relevant example, Simpson et
 5 *al.* [73] showed that the incorporation of 45S5 and ICIE4 in PLGA (95/5) did not generate the same tensile and
 6 compressive properties. While ICIE4-based composites showed significant increases in Young's modulus and compressive
 7 strength and a slight reduction in tensile strength, the modulus of 45S5-based composites remained substantially
 8 unchanged, while its ultimate strengths, both compressive and tensile, were severely reduced (Table 5). In Figure 13 the
 9 evolution of the MW of PLGA in 45S5-based composites is shown. Considering that the particle size (D_{50}) of 45S5 and
 10 ICIE4 were 35.3 μm and 5.2 μm , respectively, the authors pointed out how the influence of the glass composition is higher
 11 than the one of granulometry [73]. 45S5 and ICIE4 have comparable network connectivity ($\text{NC} = 2.12$), but the sodium
 12 content of ICIE4 is one fourth of the one in 45S5 (6.6 mol.% instead of 24.4 mol.%), which drastically reduces the
 13 reactivity of the former and, in turn, the aggressiveness it has towards the polymer matrix.

14 **Table 5:** Summary of the mechanical properties of ICIE4-PLGA and 45S5-PLGA compared to a neat PLGA control. The degradation of
 15 the mechanical parameters is way more severe in the case of the addition of 45S5 particles.

	PLGA	ICIE4-PLGA	45S5-PLGA
Young's modulus (GPa)	3.4	5.9	3.5
Tensile strength (MPa)	65.3	35.8	< 1.0
Compressive strength (MPa)	92.3	93.1	69.0

16



17

18 **Figure 13:** Evolution of the molecular weight of the PLGA and the composite based on PLGA and 45S5 (PLG4B) et ICIE4 (PLGIB) after
 19 each step of the production of the samples (adapted from [73])

20 In a similar study, the same trend was confirmed when investigating the impact of granulometry, sodium and phosphor
 21 contents and NC on the final properties of several composites with various BG compositions incorporated up to 25 wt. % in
 22 a P(L/D,L)LA (70/30) matrix [158]. Figure 14 summarizes the current knowledge and challenges related to the reactions
 23 happening at the interface between BGs and polyesters.

THE BIOACTIVE GLASS/POLYESTER INTERFACE

Bioactive glass fillers can degrade the matrix

The addition of BG often negatively affects the MW, thermal behavior and mechanical properties of the polyester matrix

Key variables

- BG composition
- Particle shape and size
- Amount of filler

What happens following filler incorporation?

- SiO⁻ groups in BG break ester bonds in the polymer
- BG hydrophilicity leads to water adsorption and catalyzes hydrolysis
- Highly reactive BGs dissolve faster and alkalize the environment, favoring polymer degradation
- Voids tend to form at the matrix/filler interface, resulting in reduced mechanical properties
- Low particle size causes higher and more distributed degradation
- High particle size causes large localized matrix defects.

1

2 **Figure 14:** Summary of the key properties and challenges of the filler/matrix interface in composites fabricated using polyesters and
3 BGs.

4 5.3 Properties and characterization

5 5.3.1 Degradation mechanism of composites

6 The degradation behavior of polyester/BG composites is a complex phenomenon resulting from the combination of the
7 degradation kinetics of its two components and their interplays (Figure 15). On one hand BGs usually are characterized by
8 a relatively faster degradation that increases the pH as a consequence of cation release, on the other side polymers slowly
9 degrade hydrolytically and induce a drop in pH. The immersion medium will change accordingly: right after immersion the
10 pH usually increases due to the BG dissolution. However, at the onset of hydrolysis, it will quickly decrease [141,158]. In
11 some cases, it has been reported, that if it is correctly tailored, the degradation of the BG could neutralize the acid
12 degradation by-products of the polyester and even increase the overall pH of the medium [60,61]. Moreover, according to
13 some authors, the presence of defects from composite fabrication (i.e. pores and cracks) as well as of voids left from BG
14 particles degrading could aid the evacuation of acidic by-products from the bulk of the composite [141,142]. This in turns
15 reduces autocatalysis and the formation of hollow structures typical of bulky polyester devices [83,239,271].

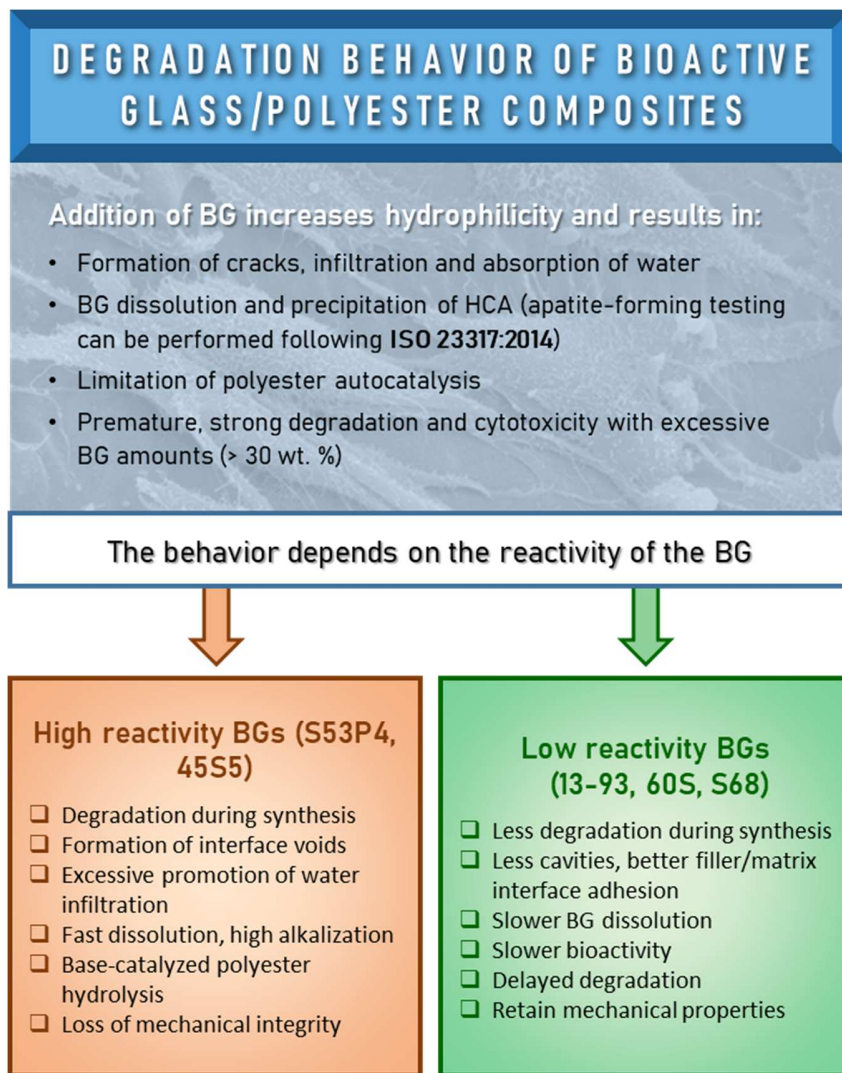


Figure 15: Summary of the most important characteristics of the degradation behavior of polyester/BG composites.

Other studies pointed out that the presence of cavities in together with the hydrophilic nature of BGs favor the infiltration and absorption of water and therefore the hydrolysis catalyzed by the formation of alkaline microenvironments known to increase the erosion of the polyesters [73,85,157,158]. This occurs particularly at high BG mass fractions and with highly reactive compositions. For instance, using 45S5 or S53P4, the filler was found to promote the base-catalyzed hydrolysis of the matrix, resulting in higher MW reduction, swelling and mass loss in the composite compared to a neat polymer control [60,73,74,93,98,141,142,157,158,168,239]. Vice versa, when using more stable compositions (e.g. 13-93, 60S) the degradation rate of the polymer is not increased by the dissolution of the BG [157,158,168]. For example the immersion in PBS of a 13-93- P(L/D,L)LA (70/30) for 87 weeks resulted in a negligible MW variation [168]. Thanks to its low sodium content and high network connectivity (2.6), 13-93 dissolves very slowly and does not damage. Generally, all studies perform on the topic point out that the degradation behavior of a final composite can especially vary as a function of the filler/matrix ratio, the granulometry and the composition of BG. BGs and polyesters are characterized by behaviors that

1 could possibly detrimental to each other when combined. However, with careful tailoring the negative effects can be
2 neutralized, leading to the fabrication of materials with high control in terms of degradation behavior compared to its
3 constituting components [158].

4 5.3.3 Mechanical properties

5 Composite fabrication methods can degrade the polymer matrix of the composite, resulting in reduced mechanical
6 properties compared to the respective neat polymer. In particular, a main focus of research in this sense is the assessment of
7 mechanical properties after an *in vitro* degradation study that mimics the biological environment. After incubation,
8 regardless of the BG composition, the majority of studies reports significantly lower mechanical properties of the
9 composite when compared to a polymeric control [73,74,140,141,158]. In a relevant study, a 45S5-P(L/D,L)LA (70/30)
10 composite lost 60% of its compressive strength showed that after 14 days of *in vitro* immersion in PBS. On the contrary,
11 the mechanical properties of a polymer control were not affected [74]. Similarly, Zhou [157] reported a 22% reduction in
12 bending strength (from 74.2 to 58.2 MPa) when a low reactive BG (i.e. 60S) was added to PLLA and incubated for 20
13 weeks. Niemela et al. [142] offered a possible solution to this issue, showing that it is possible to obtain a self-reinforced
14 composite made of 20 wt. % of 13-93 BG and a P(L/D,L)LA (70/30) having better shear and flexural properties than the
15 neat polymer even after 36 weeks of immersion in PBS. Although the shear properties of the composite are 23% lower than
16 that of the P(L/D,L)LA (70/30) before the immersion, its shear properties decrease from 81 MPa to 62 MPa while that of
17 the polymer drop from 106 MPa to 8 MPa. The amount of BG seems to be a decisive factor: when 30 wt. % 13-93 is added
18 to the composite, the mechanical properties decreased below 30 MPa at the end of testing. The use of a filler with different
19 aspect ratio (e.g. fibers) seems to be another viable strategy to improve the mechanical properties of composite and to
20 achieve an anisotropic behavior that mimics the one of bone [272].

21 5.3.1 Apatite forming ability assessment

22 Similarly to tissue engineering scaffolds, triggering the nucleation of HCA and enhancing bonding with bone is the key
23 element for the success of molded implants. Generally, the higher the amount of BG, the greater the amount and faster the
24 rate of HCA formation. However, high BG loading also leads to premature degradation of the composite with the
25 appearance of cracks, as previously discussed. A good compromise between the two properties should be sought according
26 to the final application. The evaluation of bioactivity is most commonly carried out *in vitro* using physiological-like fluids.
27 The most common are Simulated Body Fluid (SBF), Buffered Saline phosphate (PBS) and Tris. When immersed, BG is
28 able to induce the precipitation of HCA at the surface and in the composite. During and after immersion, the variation in
29 morphological, mass, and mechanical properties of the composite can be assessed to obtain measurements of the
30 performance of the material. Depending on both the BG and medium composition, as well as the overall degradation rate of
31 the composite, the precipitation can be more or less rapid and result in various crystal morphologies [85,273]. As
32 previously mentioned, 45S5 and S53P4 are highly reactive: they dissolve rapidly, inducing the precipitation of calcium
33 phosphates. It was observed that calcium phosphates precipitate within one week. In particular, the precipitation occurs at
34 the polymer/BG interface when the test is performed in PBS or Tris and on the surface of the composite when immersed in
35 SBF. This probably happens because of the cavities initially present in 45S5 and S53P4 composite as a consequence of
36 their processing: the defects in the material determine the accumulation of water around the BG particles, followed by

1 alkalization of the environment. This phenomenon is less pronounced in SBF due to its higher buffer capability and as such
2 determines a difference in where the precipitation takes place. The less reactive formulation S68 was also tested. Its slower
3 dissolution resulted in less marked precipitation: after two weeks of immersion a thin layer of HCA was observed at the
4 filler/matrix interface when using SBF and PBS, but not with Tris. Besides calcium phosphates, other phases can also form.
5 Ginsac *et al.* [98] observed the deposition of a layer of calcite (CaCO_3) in addition to the formation of HCA when testing
6 45S5/P(L/D,L)LA (70/30) composite by immersion in SBF. The authors suggest that this probably happened because of the
7 strong release of Ca^{2+} ions occurring at the early stages of 45S5 dissolution. However, it was also noted that the
8 crystallization of calcite and HCA are two independent parallel phenomena [98,158]. The presence of calcite does not
9 hinder the crystallization of HCA and, as such, does not reduce the bioactivity of a composite. Furthermore, it has been
10 reported that even for less reactive BG formulations, a phosphate calcium (HCA or phosphate octa calcium) layer could
11 cover almost all the external surface of the composite and not only the regions next to the BG particles [158].

12 **5.4 *In vitro* and *in vivo* biological testing**

13 Few studies report on the *in vitro* biocompatibility tests for molded implants. The composite elaboration may introduce
14 several sources of concerns for cells and tissues, including the use of solvents and the formation of by-products of thermal
15 degradation, that have to be carefully weighed. Some authors [61] suggest that there is an optimal threshold for the BG rate
16 for osteoblastic growth. Composites based on P(L/D,L)LA (70/30) loaded with increasing amounts of 45S5 (i.e. 20, 30 and
17 50 wt. %) and elaborated by solvent casting plus injection molding did not show any relevant cytotoxic effect on MG63
18 osteoblastic cells after 10 days of culture [74,141]. A slight decrease in cell viability was observed in the case of the 50 wt.
19 % composite, corroborating the claim of an optimal quantity of BG. In another relevant study [274], the macrophage
20 response toward silane grafted 45S5/PCL (45 wt. % of glass) composite molded fibers was deemed negligible after 48 h,
21 with craniofacial osteoblastic cells optimally attaching and spreading.

22 In parallel to and after *in vitro* testing, *in vivo* implantation is often performed. Most reports investigating the effects of the
23 *in vivo* implantations of polyester/BG composites agree on their good biocompatibility [74,143,168,275]. For instance,
24 Tuomo *et al.* [276] confirmed the satisfactory osteointegration of P(L/D,L)LA (70/30) and 13-93 composites with 20 wt. %
25 BG. The implantation was performed introducing osteotomies in the distal part of rat femurs. After one week, assays for
26 bone grip and newly formed bone were performed with promising results. After 24 weeks, radiological analysis confirmed
27 that all implants were fully recovered. Finally, after 52 weeks, animals were sacrificed to find out that newly formed bone
28 was present on all samples, with minor formation of granular tissue in 30% of cases. All osteotomies were stable,
29 confirming the good performance of the composite. In addition, the presence of granulation was not considered critical as it
30 could be deemed not chronic and ascribed to the physiological healing process [143,168,276]. Similarly, the behavior of a
31 30 wt. % 45S5/ P(L/D,L)LA (70/30) composite was investigated using a rabbit femoral condyle model [74,141].
32 Cylindrical implants were inserted into critical size bone defects and evaluated at 1 and 6 months. After one month,
33 preliminary osteointegration was superior in the composite, when compared to a polymeric control. At the end of 6 months,
34 similarly good tissue response without chronic inflammation was confirmed for both materials. The lack of significant
35 difference in biological response due to presence of BG is rather unexpected and highlights a typical limit of *in vivo*
36 testing: its results are complex and often hard to interpret. In a follow up study, a similar 45S5/P(L/D,L)LA (70/30) was
37 prepared using a BG with finely controlled particle size ($D_{50} = 5 \mu\text{m}$). Composite and polyester interference screws were

1 developed and implanted in sheep condyles for 3 and 6 months. The hollowness of these implants allows a more detailed
2 analysis of the behavior of the materials *in vivo*, enhancing their degradation. Remarkably, after 6 months the inner and
3 outer surfaces of the composite screw were surrounded by newly formed bone, while the polymer screw is only partially
4 colonized by cells due to its inferior bioactivity (Figure 16). In particular, cells were not able to successfully colonize the
5 inner part of the implant. The presence of BG is therefore crucial for a rapid and effective regeneration of the bone. The
6 disadvantage is that often the mechanical properties decrease faster *in vivo* in the case of composites. This phenomenon
7 was reported by the results of Niiranen *et al.* [168], showing that after 24 weeks of subcutaneous implantation in a rat
8 model the decrease in mechanical properties for composite samples is higher than the one of a relevant control. The
9 mechanical strength could be possibly improved by decreasing the level of BG to 15 wt. % and optimizing the particle
10 shape [168,264]. In another study, the mechanical and degradative properties of poly(L-co-D,L-lactic acid)/silicate
11 bioactive glass fibers (PLDLA/SGFs) composite pins were tested *in vivo* by insertion into the erector spinae muscles and
12 femurs of beagle dogs. Samples were harvested 6, 12, 16, 26, 52, 78, and 104 weeks to investigate bone formation by μ CT
13 and their shear strength mechanical properties. The materials were also characterized by TGA, DSC and GPC. The
14 composite approach resulted in stronger pins that were stable beyond 26 weeks and improved bone formation already 52
15 weeks, thanks to the degradation products released from the bioactive glass fibers. PLDLA/SGFs composite pins had
16 higher initial shear strength and were relatively stable for at least 26 weeks [277].



17

18 **Figure 16:** Comparative histological analysis of 100% polymer screws versus composite screws, both implanted *in vivo* in sheep
19 condyles (image courtesy of Noraker, France)

20 *In vitro* and *in vivo* testing offer very insightful information about the biological performance of composites and, more
21 broadly, biomaterials. However, they both have important limitations that have to be taken in consideration when using
22 these models. This disadvantages also contribute to make these two models work more effectively when used together.
23 When comparing *in vitro* to *in vivo*, one of their major difference is the environment they offer and how this influences the
24 degradation behavior of the biomaterial. The degradation can ultimately have major consequences on the biocompatibility
25 of the implant. On one hand, *in vitro* testing subjects the material to an amplified hydrolytic stress: phenomena such as pH
26 variations or local concentration of by-products tend to be overexpressed and increase the hydrolysis of the polymer. On
27 the contrary, when implanted *in vivo* the material is less affected by hydrolysis because of the surrounding bone tissue and
28 its strong homeostasis. Nevertheless, the *in vivo* environment can increase the degradation rate as a consequence of
29 biochemical (i.e. enzymes, cells) or physical complications (e.g. mechanical stimulation of the implant). Comparative
30 studies were carried out to evaluated difference in degradation and mechanical properties after *in vitro* and *in vivo*

1 incubation [143,168]. The results showed after 24 weeks showed a remarkable difference between the two models. In
2 particular, *in vivo* implantation in rat seemed to offer a significantly more aggressive environment, which resulted in
3 decrease in bending strength of 70% compared to 49% *in vitro* and in shear strength of 68% compared to 37% *in vitro*. The
4 first structural changes due to degradation were seen at 24 weeks *in vitro* and 3 weeks *in vivo*. At 36 weeks, implants *in*
5 *vivo* did not offer enough integrity to allow mechanical testing. Partially in disagreement with these results, Kharazi et al.
6 [278] did not assess significant differences between the degradation behavior *in vitro* and *in vivo* on a similar PLLA/BG
7 system for orthopedic fixation, perhaps due to the different form of bioactive glass used (i.e. braided fibers). These results
8 highlight the complexity and plethora of variables to face when analyzing the biological performance of biocomposites and
9 how the careful interpretation and comparison of results is mandatory to obtain insightful information and fabricate
10 successful biomedical devices. In other words, the information obtained from a single study always has a high risk of being
11 highly misleading. Only the compilation of numerous data can permit to reach a comprehensive understanding of the
12 biocompatibility and biological behavior of bioactive composites. Future studies should focus on gathering an extensive
13 pool of data and expanding the knowledge *in vitro* and *in vivo* behavior of these composites. An increase in the statistical
14 relevance of results would consecutively give a better substrate of understanding to develop insightful and safe clinical
15 trials.

16 **6. Discussion and conclusions**

17 Bioactive and bioresorbable composites fabricated using aliphatic polyesters and bioactive glasses represent an important
18 class of biomaterials than combine the advantageous properties of the organic and inorganic materials. They are considered
19 great candidates for orthopedics and bone tissue engineering thanks to the numerous beneficial properties that they can
20 offer by exploiting and combining the key properties of the constituents. In the past decades, scientific research intended to
21 optimize the properties of polyester/BG composites and consolidate their application in biomedicine, in particular as bone
22 implants or scaffolds. Such composites exhibit tailorable degradation, biocompatibility, non-toxicity, and complete
23 bioresorbability. Moreover they can provide bone healing capability and antibacterial effects (i.e. mainly via therapeutic ion
24 release from the BG component). Furthermore, polyester/BG composites are scalable, reproducible and easy to process.
25 The fabrication of bone tissue engineering scaffolds can be carried out by a wide range of techniques and methods suitable
26 to prepare porous structures with complex porous geometry that has to be hierarchical and interconnected. Furthermore,
27 several key physical, chemical and biological properties have to be taken into consideration. The design of a proper
28 construct (scaffold) requires understanding its structure and careful balancing of topographical, mechanical and biological
29 characteristics. The field of biomedical polyester/bioactive glass composites is constantly pushing the boundaries of
30 materials characterization. Nonetheless, while polyester/BG biomaterials successfully solved some clinical aspects, others
31 still remain to be tackled, especially for high-performance load bearing applications. As a matter of fact, the achievement of
32 adequate (time dependent) mechanical properties of polyester/BG porous scaffolds remains one of the main challenges of
33 this technology. This limitation can be in principle tackled following two approaches. The current surgical approach
34 consists in pairing the bone filler material (for its bioactive and osteogenic potential) with strong orthopedic fixation
35 devices that can bear the load. On the other hand, the biomaterial research approach is looking into novel processing
36 techniques that should result in tougher and mechanically robust scaffolds. Following this direction, additive

1 manufacturing, and robocasting in particular, seem to be the most promising technique to obtain polyester/BG-based
2 scaffolds with superior mechanical properties. Key challenges for the near future seem to be the optimization of the
3 topographical resolution that can be reached and the engineering of complex systems containing cells and active
4 biomolecules. In parallel, the characterization of these constructs has to improve and evolve together with the development
5 of new materials and scaffolds. New standards have to be implemented, both for physicochemical and bioactivity testing
6 and for *in vitro* cell culture. At the same time, an agreement should be reached on what are the best *in vivo* models suitable
7 to test such biodegradable and bioreactive materials and allow comparison between different composites and structure at
8 minimum number of animal tests.

9 Meanwhile, the preparation of molded composite implants via the solvent route or the thermomechanical methods has also
10 been widely explored. In this case, the main issue is the drop in molecular weight that the matrix of the composite suffers as
11 a consequence of the harsh processing conditions. Milling, high temperature and pressure, the presence of water and the use
12 of solvents can all contribute to the MW drop. In addition, BG particles can interact with the polyester and catalyze its
13 degradation. BG adsorbs water, alkalizes the environment and promotes hydrolysis. For silicate-based glasses, SiO₂ groups
14 can attack the ester linkages of polyesters, especially at high temperatures. The polyester/BG interface still remains a major
15 thread to the successful fabrication and application of thermoformed polyester/BG composites. If not properly designed,
16 composites can be characterized by low interface adhesion and formation of holes and cavities that can ultimately
17 drastically decrease the properties of the final material. Since the interface properties mainly depend on the BG
18 formulation, careful tailoring of the glass composition as well as investigation into possible strategies for interface
19 optimization (e.g. chemical grafting) are important directions for future research in order to obtain a homogeneous and
20 reliable composite. In addition, changing the filler-to-matrix ratio and using self-reinforcing techniques are alternative
21 investigated routes to reduce the BG degradation rate and achieve superior mechanical properties. Generally, the BG
22 composition is the decisive factor to determine mostly every property of a composite. In particular, the overall degradation
23 of the composite highly depends on the reactivity of the glass: a more reactive BG is usually more bioactive but also a more
24 “aggressive” glass, which dissolves fast and induces strong alkalization. An alkaline environment is then a very effective
25 catalyzer for hydrolysis. Using less reactive BGs was identified as a promising strategy for the fabrication of composites
26 with interesting properties: better BG/polyester interface properties, with good interaction between the two phases and
27 moderate environmental changes upon immersion in physiological-like fluids. As a result, high matrix degradation rates are
28 avoided and, ultimately, the thermal and mechanical properties are improved over standard-45S5 BG-based composites.
29 With these composites, bioactivity is slowed down, but not hindered, as confirmed by successful *in vitro* and *in vivo*
30 biological testing comprehensively discussed in this review. In particular, their mechanical properties approach those of
31 natural bone, making them very attractive material systems to tackle the problem of stress shielding at the bone/implant
32 interface. Moreover, the composites are excellent candidates for the development of tailorable osteosynthesis devices for
33 load bearing applications, as the analysis of literature reveals. Recently, new strategies for the optimization of traditional
34 composites are also under investigation. Among others, nanocomposites [58] and organic/inorganic hybrids [10] are two
35 families of materials born as natural evolution of traditional composites, mostly relying on sol-gel based processing [279].
36 Both nanocomposites and hybrids show promising improved properties, although they are still at a relatively early stage of
37 development and further research is needed to effectively turn these results into available products. Based on the very large

1 amount of critical data and the decades of experience on the topic, the authors anticipate that polyester/BG composite
2 combinations with different types of polymers and BGs will continue to attract the interest of the scientific community and
3 potentially also by the medical market. In particular, next investigations should place the focus on clinical and translational
4 aspects. For a successful expansion of the industrial application of polyester/BG composites, three main challenges will
5 have to be tackled: (i) increase of the scalability and reproducibility of composites through the choice of polymer/BG
6 combinations that show consistent degradative, mechanical and interfacial properties (avoiding glass crystallization and
7 premature polymer degradation in particular), (ii) achievement of a better understanding of the in vivo behavior of these
8 devices by increasing the available data on the interaction between composites and host organism and (iii) translation of
9 these key findings to meet regulatory needs. Future research into polyester/BG composites will have to move in multiple
10 directions and simultaneously foster the various strategies mentioned above. On one hand, an industrial approach should
11 focus on scalability, reproducibility and regulation of current robust material technologies (i.e. conventional composites). In
12 parallel, scientific research will develop new biomaterial technologies, including nanocomposites and hybrids, which
13 should contribute to expand the applications of polyester/BG composites in a range of biomedical sectors.

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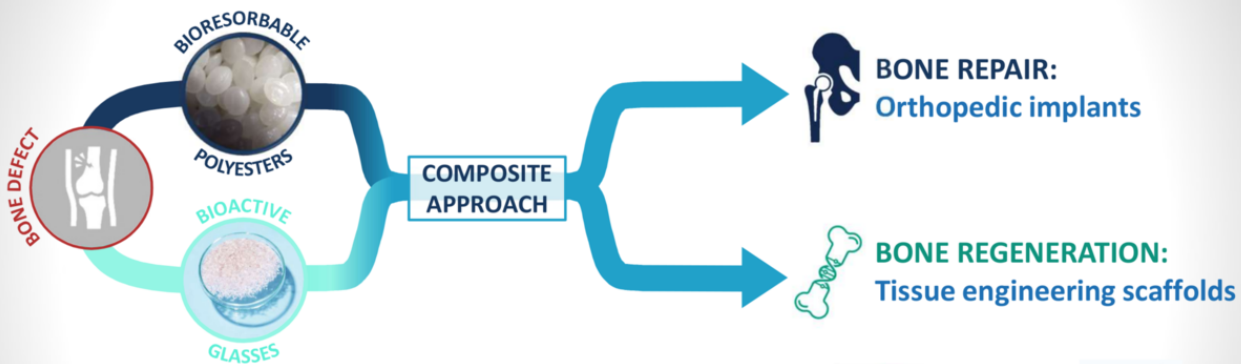
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