

The Role of 3D Modelling and Printing in Orthopaedic Tissue Engineering: A Review of the Current Literature

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ABSTRACT

Orthopaedic surgery lends itself well to advances in technology. An area of interest and ongoing research is that of the production of scaffolds for use in trauma and elective surgery. 3D printing provides unprecedented accuracy in terms of micro- and macro-structure and geometry for scaffold production. It can also be utilised to construct scaffolds of a variety of different materials and more recently has allowed for the construction of bio-implants which recapitulate bone and cartilage tissue. This review seeks to look at the various methods of 3DP, the materials used, elements of functionality and design, as well as modifications to increase the biomechanics and bioactivity of 3DP scaffolds.

KEYWORDS: 3D printing, Rapid prototyping, bone scaffold, orthopaedic implant

INTRODUCTION

3D printing (3DP), synonymous with rapid-prototyping as well as additive manufacturing, is the process whereby a 3D rendered image is used to create physical models. It has become a widely accepted and predictable method of creating bespoke prostheses, models for operative planning and simulation as well as scaffolds for tissue engineering.

Initially a 3D model is constructed through computer-aided design or modelling software. The rendering is subsequently divided into finely sliced cross sections which are consequently printed. There are a variety of methods of 3DP. These include selective laser sintering (SLS), stereolithography (SLA), fused deposition modelling (FDM) and direct metal laser sintering (DMLS) [1].

SLS uses a carbon dioxide laser to coalesce and thereby sinterize the printing material through the application of both thermal and laser energy. The powdered printer material is thereby heated to melting point causing the particles to fuse together to form a shape in a thin slice-by-slice manner [2]. DMLS is a similar process that uses an Ytterbium laser to fuse metal powder into a solid part by melting it locally.

SLA uses photopolymerisation, whereby each successive slice of the 3D model is constructed through exposure of the printing material to ultraviolet or visible light. The printing material used is commonly a photoreactive liquid resin which, when it solidifies, generates a structure with the appropriate 3D micro- and macrostructure required [3].

FDM relies on extrusion of a thermoplastic filament through a temperature controlled extruder. The resultant semimolten polymer is then sequentially lowered and the next layer placed on top as it dries. This is the most commonly used method in most commercial systems [4].

In the context of tissue engineering, this provides a paradigm leap. The precision, reproducibility and ability to construct a unique and patient specific implant are paramount in the success of this method.

In the context of orthopaedic tissue engineering, the primary role of 3DP is to construct scaffolds. These act as templates for cell migration, adhesion and eventual maturation within an existing or surgically created defect. According to Hutmacher [5] a scaffold should be capable of the five following criteria:

1. Display properties of bioresorption within the tissues they inserted into
2. Display properties of biocompatibility within the tissues they inserted into
3. They should display the biochemical properties necessary for cell attachment, growth and differentiation
4. They should have the appropriate porosity (pore size, pore shape and interconnecting pore size) to allow for the construction of an interconnected porous network for cell growth and nutrient exchange
5. They have the appropriate 3D shape and structure to adequately match the defect into which they are being implanted

In addition to this, in the context of scaffolds for bone and cartilage defects, it should also create a stable interface with the host bone without formation of scar tissue. It should also allow for mechanical properties similar to bone or cartilage as well as being able to be appropriately sterilised prior to implantation.

Of obvious importance are the biomechanical properties of the scaffold used. Regardless of the material used, the more rigid and solid a scaffold is, the abler it will be to sustain the mechanical forces required of it. Inversely the more porous and flexible a scaffold is, the more likely it is to allow integration and proliferation of cells. As such, there needs to be a compromise between these two for a successful scaffold to be constructed.

Returning to porosity, the minimum pore size acceptable for appropriate bone ingrowth is 100-150 μ m, with most current fabricated scaffolds having porosity between 150-500 μ m.

Conventionally, scaffolds were constructed via several methods including particulate leaching [6], freeze drying [7], foaming [8], emulsification [9], thermally induced phase separation [10] and electrospinning [11].

The main problem with all of these technologies was the inability to precisely control shape, porosity and adequate biochemical properties which all define the scaffolds capability for defect integration and cell integration. 3DP overcomes these issues.

METHODS

One author reviewed the relevant literature. A total of 102 Articles were found of which 65 met the criteria for use.

PRINCIPLES

There exist several reasons why a bone or cartilaginous defect, whether post-traumatic, intra-operative or pathological, may fail to heal appropriately. In these cases, the previous gold-standard has been the utilisation of autologous bone grafting, since these are inherently osteogenic (i.e. contain living cells able to proliferate and differentiate), osteoinductive (i.e. the ability to induce progenitor cells to differentiate into mature cells lines) and osteoconductive (can generate new bone by acting as a scaffold for bone ingrowth). The principles are similar for a cartilaginous graft.

There is, however, a 30% complication rate associated with autologous grafts, including, donor site morbidity and pain, increased infection risk and likelihood of haematoma development. The risks of allograft are similar with the added risks of disease transmission from the donor to recipient. They also have to undergo various processes including irradiation, lyophilisation or freeze-drying to remove any immunogenic or pathogenic proteins [12].

This has paved the way for the development of synthetic grafts, with 3DP allowing for unprecedented accuracy in terms of scaffold micro- and macrostructure. This review aims to assess the research in progress with the variety of materials being used.

MATERIALS

Titanium and Other Metal Alloys

No material is more synonymous with orthopaedic reconstructive surgery than metal. This is not without good reason, metals have outstanding mechanical-strength and resilience, making them excellent choices for load bearing orthopaedic implants with tolerable longevity.

Titanium and its alloys are a wonderful example of this, with its inherent biocompatibility and enviable mechanical properties. Li et al [13] utilised 3DP technology (in their paper a hybrid combining features of DLMS and FDM which they have termed “3D fiber deposition”) to construct 5 different titanium alloy scaffolds with varying porosity. There were low porosity (3DFL- 200 μm fibre spacing), middle porosity (3DF- 500 μm fibre spacing), high porosity (3DFH – 800 μm fibre spacing), double-layered (3DFDL – 500 μm fibre spacing) and gradient porosity (3DFG – 800 to 200 μm bottom to top fibre spacing). Three of each type of scaffold (of $4 \times 7 \times 8 \text{mm}^3$) were subsequently inserted into a cage made of titanium.

These were subsequently implanted into decorticated transverse processes of the lumbar spines of 10 goats, with bone formation monitored over time through the use of fluorochrome markers. 12 weeks following implantation, they removed the implants and studied the degree of bone formation present. The constructed scaffolds were found to be biocompatible, with no evidence of toxicity or peri-implant inflammation evident. They also found that 3DP allowed for accurate porosity.

They found that the scaffold with the smallest pore size (3DFL) had the least bony ingrowth with that with the highest porosity (3DFH) had the most. Of note, the difference between 3DF and 3DFH were not statistically significant, showing that porosity is important up to a certain point (i.e. 500 μm is

nearly as effective as 800 μm in terms of bone ingrowth). Of note, the double layered construct (3DFDL) demonstrated greater bone ingrowth than 3DF, owing to its larger surface area for bony ingrowth, despite similar porosity).

As such, it seems likely, that in titanium implants, a pore size of 500 μm is ideal in terms of retaining some rigidity and thereby mechanical strength whilst allowing for near optimal bony ingrowth. A double layered structure is also beneficial by increasing the surface area available. They found that there was little bony contact or formation near the allow surface itself, due to the biological inertness of titanium. It may therefore be beneficial to coat the scaffolds with ceramic or HA to increase the bioactivity [14, 15].

Another exciting advantage of 3DP is that the implant is not required to be homogenous in terms of shape: It can be printed to fit a specific defect. Sumida et al. [16] have done interesting work which demonstrates that their 3DP titanium mesh devices for bone-augmentation had significant advantages over commercial titanium meshes which must be bent intra-operatively. They found that the custom made devices, constructed through DLMS, provided shorter operative times, with a lower degree of post-operative infection in the custom-made implant group as well. They also required fewer screws for fixation than the conventional mesh group.

Titanium is a metal and, as a metal, it relies on the basic principles of metallurgy. One of these is that the temperature at which the metal is heated during the smelting and cast process is integral to defining the characteristics of that metal. Work by Gagg et al. [17] looks into the effects of sintering temperature on the biomechanics and morphology of a titanium implant. One factor is shrinking. This is inherent to the process of DLMS. The study found that this was reduced to approximately 21% at temperatures of 1110°C or below, but in excess of 33% above temperatures of 1110°C. They concluded that this can be estimated prior to printing and prepared for.

The effect on mechanical strength was also assessed. They found that there was very little change in the young's modulus across all temperatures, and that this was more dependent on porosity than sintering temperature. The yield strength, however, was demonstrably higher with a higher sintering temperature. They therefore concluded that a sintering period of around 2 hours with a minimum of 1300°C was ideal in terms of enhancing the biomechanical properties of the implant.

Most of the studies we have examined are based on DLMS printing, however, FDM is another important area of research and development. The argument for this technology is that it has enhanced control of the fabrication process with subsequent accuracy of both macro and microstructure. They created a "slurry" of Titanium alloy ($\text{Ti}_6\text{Al}_4\text{V}$) and methylcellulose and stearic acid as binders and dispersants, with 66% titanium powder concentration. The slurry was then extruded through plastic syringes onto the platform to create a scaffold layer by layer. After the fibre deposition was completed, the scaffold was then dried at room temperature followed by heating at 50°C and subsequent sintering at 1250°C.

The study proposes a number of advantages of this method over DLMS alone. They found it was more accurate in terms of the production of complex geometry through the variability of fibre spacing, layer thickness and fibre orientation. They also relate that there the structure has the sufficient strength and rigidity to maintain its shape during construction, not requiring any suspension or support. Finally, they relate that the technology can be used with a variety of

materials, so the same machine can theoretically be used for titanium, ceramic or polymers or a hybrid composite.

An alternative technique uses FDM to construct a sacrificial wax template, which is subsequently filled with titanium slurry through conventional powder metallurgy techniques [18]. The researching team then went on to culture pre-osteoblast cells with cell proliferation determined by DNA analysis. They found that a compaction pressure of 250MPa and sintering temperature of 1300°C (similar to the studies mentioned above) yielded the highest strength scaffolds. The porosity was developed at 66.8% (equivalent to average pore sizes between 400-500 μm) which yielded a Young's modulus of almost 20.5 GPa in the axial direction and almost 4.35 in the transverse direction, significantly higher than trabecular bone (between 0.1-10.4 GPa) [19]. They obtained encouraging results, with adequate growth of pre-osteoblast cells on the surface of their scaffolds. This is therefore another very promising technique.

As mentioned earlier, titanium is a biologically inert material. As such an ideal scaffold would utilise titanium's inherent mechanical properties but enhance the biological activity through application of more active media. Lopez et al. [20] electrodeposited their titanium scaffolds with Calcium phosphate (CaP) to increase their biological activity. This was carried out to augment the osteoconductive properties of the implant by reducing inertness and increasing surface area. Furthermore, they seeded their implants with mesenchymal stem cells (MSC) harvested from the femur of 4 week-old rats. After 3 days the MSC impregnated scaffolds were implanted into the dorsal subcutaneous pouches of rats. They inserted uncoated titanium scaffolds, CaP coated scaffolds and finally the MSC impregnated CaP coated scaffolds.

To typify their scaffolds, the average scaffolds porosity was 50% with consequent pore sizes of 1000 μm , larger than most of our previously discussed studies. This led to a compressive strength of almost 95 MPa and Young's modulus of 12.5GPa. Unfortunately, despite the promising hypothesis of increased cell growth and osteoinduction on the coated and particularly MSC impregnated scaffolds, all scaffolds demonstrated similar results, with the presence of fibrous tissue encapsulation with orientated collagen fibres and mineralisation. However, this mineralisation lacked osteocyte lacunae, present in mineralised bone tissue. This may be explained by the relatively short sampling date (4 weeks post implantation).

Work by Maleksaeedi et al. [21] utilised similar methods to our previous studies (FDM printing of a titanium/PVA mixture followed by sintering by an argon laser at 1000-1350°C). Where their work differs, is in the modification of their internal channels and thereby pores. They firstly coated the titanium with the more hydrophilic titanium oxide, using hydrothermal treatment. This reduced the biological inertness of titanium. The scaffold was then electrochemically coated with a hydroxyapatite precipitation. They demonstrated that this increased the bioactivity and surface area of the scaffold, however they failed to test the in-vivo/vitro effects of their scaffolds, stating that the technique requires further validation on animal models.

As demonstrated above, titanium is a very versatile and appropriate choice for scaffolding. It is, however, not the only one. Lai et al. [22] constructed a scaffold consisting of poly lactide-co-glycolide (PLGA), beta-tricalcium phosphate (TCP) and magnesium (Mg). This was fabricated using low temperature rapid-prototyping (FDM), yielding macropores of 450 μm and micropores between 2.5-90 μm with an overall porosity of 85% on micro-computed tomography study. They yielded a

Young's modulus of 104MPa in the 15% Mg scaffolds. They impregnated the scaffolds with osteoblasts and demonstrated favourable proliferation of cells in their scaffolds after a 7 day culture. Of note this results were only favourable in the scaffolds containing Mg and not those which were constructed purely of TCP-PLGA. As such they were able to conclude that Mg demonstrates favourable osteoinductive properties, a property lacking in titanium alloys.

Bioglasses

Historically, bioglasses have been limited in their use as scaffolds due to their lower mechanical strength and resistance to fatigue failure. It is only recently that bioglasses have been constructed with similar compressive strengths to trabecular and cortical bone.

What has been known is that bioglasses integrate well with host bone and soft tissue [23] as established by the advent of 45S5 bioglasses by Hench. They also demonstrate favourable qualities in terms of cell migration and proliferation [24]. This is in a large part due to the inherent properties of the bioglass construct to react leading to the formation of calcium compounds on their surface (largely HA or amorphous calcium phosphate) as well as their ability to alter the ionic composition of tissue leading to osteogenesis [25] and angiogenesis [26]. Their composition can also be altered to adjust their degradability.

In terms of porosity, an overall porosity of >50% with pores of 100 μm is desirable [27,28]. Other methods of bioglass formation lack the accuracy and flexibility of 3DP. These include thermally induced bonding, polymer foam replication and freeze casting of suspensions.

In terms of 3DP, this is still an area in its infancy. SLS and FDM methods have both been described in the literature. In terms of the FDM method they found that after 20 days in simulated body fluid the scaffolds developed HA layer on their surface, however mechanical strength and degradation was not disclosed [29]. They found, however, that the technique allowed for enhanced precision, with lines of 30 μm possible. In terms of the SLS printed scaffolds, they were able to attain an anisotropic structure with overall compressive strength similar to cortical bone (136MPa) [30].

Whilst the compressive strength of the scaffolds is similar to that of cortical bone, their use continues to be limited by their relative brittleness and resultant propensity toward fatigue failure. An area of future development seems to be through the advent of bioglass scaffolds with a polymer coating. This improves the brittleness of the bioglass composite by enhancing energy dissipation. Until this time, this author cannot recommend their use in load bearing orthopaedic implants.

Bioceramics

CaP ceramics have the inherit properties of being osteoconductive, biocompatible as well as degrading over time. HA scaffolds, produced from coral are a prime example of organic materials and synthetic CaP scaffolds can be produced through 3DP with the attendant accuracy allowing them to mimic the microstructure of trabecular bone.

In terms of in vivo studies, both Tsurga [31] and Holmes [32] suggest a pore size of at least 200 μm with 400 optimum, in order to allow for the average osteon size of 223 μm and need for capillary bed formation. This needs to be married with the need for mechanical strength, which decreases with increased porosity, hence 300 μm is the ideal pore size recommended [33]. Work by Fierz et al. [34], focusing specifically on HA scaffolds, corroborates 300 μm as the ideal pore size.

In terms of 3DP, both SLS and FDM techniques have been employed. Habibovic et al. [35] used SLS techniques to construct brushite and monetite implants of differing geometries. These were consequently implanted into the transverse processes of L1-4 in 12 Dutch goats as well as intramuscularly. Their results were highly promising in terms of osteoinduction at 12 weeks in both monetite and brushite. Unfortunately, the overall compressive strength of the brushite was almost 21.7MPa and that of the monetite was 8.3MPa. Despite these factors, the implants did not fail in the goat transverse processes at 12 weeks.

They also found a higher rate of conversion of their implants into HA intramuscularly. This phenomenon is also described in an earlier study [36] and is thought to be attributed to the increased fluid exchange in soft tissue. This problem can be overcome by altering the composition of the CaP compound to alter the overall biodegradation of the implant.

HA itself is a very well-known and often used bioceramic in orthopaedic implants and both it and TCP have remarkably good biocompatibility and biodegradability osteoconductive properties. Work by Becker et al. [37] has compared scaffolds constructed from both, through an FDM technique. Both systems had an internal central canal to allow vascular or nerve transmission, aiding the osteogenic properties. These were then implanted intramuscularly into healthy rat specimens. These were then compared to the control, bovine HA. Overall, their CT scan densitometry results demonstrated higher osteoinduction and density in the printed HA group. They also found the addition of a central canal was of benefit in increasing the vascularity and hence viability of the new bone formed.

Addition of further compounds to the CaP ceramic matrix has also been explored. Recent work by Zhou et al. [38] has explored the addition of calcium sulphate based powder to CaP ceramics. They established significant improvements in powders constructed through this technique, with demonstrably higher compressive strength with increasing CaP:CaSO₄ ratio. In terms of the type of CaP used, Hydroxyapatite (HA):CaSO₄ powders showed better results than beta-tricalcium phosphate (β -TCP):CaSO₄ powders, corroborating the results of the study above.

Addition of zinc and silica oxide to CaP ceramics has also been explored. Work by Field et al. [39] looked at the addition of these oxides to TCP based scaffolds through a combination of FDM and SLS processes. Their results demonstrated that additions of these oxides through sintering onto the TCP scaffolds lead to an up to 2.5 fold increase in compressive strength as well as enhanced osteogenesis and scaffold mineralization. Other studies have also demonstrated that zinc increases alkaline phosphatase activity, leading to increased bone turnover and growth [40, 41] as well as increased bone ingrowth in scaffolds [42].

Addition of polymers appears to be a logical step in the construction of scaffolds, as bone is a composite of HA and collagen. In terms of composites, the ceramic is either HA or TCP (beta-tricalcium phosphate) or a combination of the two. These are then combined with bovine, porcine or

equine type 1 collagen. The commercially available products aren't at present 3DP, however this is most likely the future of 3DP scaffold technology as it most closely mimics bone, by creating scaffolds with inherent mechanical strength as well as improved energy distribution, leading to improvements in fatigue failure.

Polymers

Both natural and synthetic polymers have been utilised in the production of scaffolds. In terms of natural polymers this includes collagen (and its hydrolysed product –gelatin), chitin, chitosan, starch and chondroitin sulphate. Synthetic polymers include PCL (poly- ϵ -caprolactone), PLA (poly-lactic acid), PGA (poly-glycolic acid) and PBT (polybutylene terephthalate) [43].

Most of the current literature is based on Starch as a polymer. Starch-based polymers demonstrate good overall degradation and porosity with increasing cellular migration and proliferation, which is desirable. Lam et al [44] used a starch-based polymer composite to construct their scaffolds through FDM type techniques. They were able to demonstrate adequate porosity and compressive strengths through this method, with evident cell migration and biocompatibility of their scaffolds.

Their analysis of post-processing of scaffolds demonstrated that scaffolds with a circular pore design shrunk more than elliptical pores. They also found that treatment at 100°C for 1hr after printing helped to maintain the integrity of the scaffold, making the structure more resistant to hydrolysis and enzymatic degradation. In terms of mechanical properties, they discovered that the cylindrical shape of the scaffolds was significantly stiffer and stronger in terms of compressive strength, relative to bar and rod shaped scaffolds. Once again increasing porosity led to a reduction in stiffness. Unfortunately, they did not disclose the optimal porosity to attain cell migration and growth whilst maintaining mechanical strength.

Similarly, SLS techniques have been employed in order to fabricate starch-based composites. In a study by Samoria et al. [45] they compared the particle sizes. Smaller particles led to a denser and less porous scaffold with higher mechanical strength and young's modulus. Once again, this demonstrates that a compromise must be made between strength and porosity.

FDM has also been used to fabricate synthetic grafts. An example of this is in work by Seyednejad et al. [46] constructed PCL based and a hydroxymethylglycolide-PCL (PHMGCL) polymer scaffold which were consequently implanted into subcutaneous pouches of ten female mice. They found, not only that FDM attained accurate macro and micro-structural properties, but also that the PHMGCL degraded faster in tissue with a more profound tissue integration than the PCL grafts, showing that adding particular groups to existing polymers might enhance their bioactivity and hence success as a scaffold.

PBT is another synthetic polymer which has been used to fabricate scaffolds using FDM. Tellis et al. modelled their scaffolds on samples taken from the medial femoral condyle of an adult male hound [47]. They arranged the porosity of their scaffolds based on the bone of the dog and ensured that it closely followed that of human femoral neck trabecular cadaveric bone (71-84%) [48, 49]. They made a total of 90 scaffolds and looked at four different scaffold types by varying the geometry of the raster angles by creating alternating raster angle values leading to complex and less complex

scaffold geometries. They found that the complex interconnected pore structure group had significantly less compressive strength than that of the simple linear pore structure group, with decreases in mechanical strength in both with increasing porosity. As such, a highly organised and almost uniform scaffold pattern might be preferable to maintain mechanical strength. They also concluded that saline soaking did not affect the mechanical strength as much as in PCL based polymer scaffolds, making it preferable in en-vivo use.

True biomaterials

It stands to reason that the most viable and biologically active scaffold will contain components of human cartilage or bone, either at a macro- or microscopic level. Rapid prototyping has engendered a paradigm leap in the construction of such scaffolds.

Work by Fedorovich et al. [50] demonstrates the potential application of 3DP true-biological scaffolds. They used an FDM type technique to create hydrogel scaffolds seeded with bone marrow stromal cells (BMSCs). They found that the majority of the extruded cells survived in similar quantities to non-extruded cells. Furthermore, the cells were also able to differentiate and proliferate along their osteoblast lineage.

Building upon this technology, work by Discher et al. [51] demonstrate that the scaffold stiffness will alter the proliferation, growth and also lineage commitments of stem cells, most likely through piezoelectric properties as discussed in this review. The most commonly used scaffolds, hydrogels such as alginate or Luthrol, are far less stiff and mechanically weaker than normal bone, thereby limiting load-bearing of the graft, until they are replaced by bone or cartilage.

One way of altering the biomechanics and bioactivity of the hydrogel groups is through covalent UV cross-linking [52], as well as modification with matrix-metalloproteinase (MMP) sites, which will degrade at different rates depending on biological activity within host tissue, allowing degradation to coincide with cartilage or bone growth [53]. Further work has demonstrated that modification of hydrogels with adhesive sequences which mimic host tissue, encourage integration [54], as well as addition of CaP microparticles to promote bone formation [55]. Addition of growth factors will also encourage cell differentiation and growth, and will be discussed later in the review.

Whilst this demonstrates the viability of bone scaffolds, one area that has been fraught with difficulty in terms of repair is cartilage. This is due to the notoriously poor vascularity of host tissue, creating an environment unsuitable to scaffold integration and consequent cell growth and proliferation. Work by Shipley et al. [56] utilized cartilage cells from the donor patient and seeded these in a hydrogel scaffold, created using FDM type 3DP. The scaffolds were then enriched with nutrient rich culture media and at the same time waste material was removed, obviating the need for host blood supply. Through a series of tests and ultimately homogenization of their culture media and optimization of cell density and scaffold geometry, they were able to demonstrate that this is a promising technique for the future of cartilage repair.

This work has paved the way for more recent work by Roach et al. [57] looking at 3DP to construct osteochondral grafts for repair of a large femoral condyle defect in dogs. They used a number of techniques to ascertain the geometry of the defects, namely mode-ultrasound, MRI, CT, cryosectioning and stereophotogrammetry. They then constructed 3D models for their scaffolds

which were made to take up at least 70% of the defect area. The PDMS (poly-dimethylsiloxane) scaffolds were subsequently 3DP, through an FDM technique. This plastic scaffold was then used to construct a negative mould into which a natural polymer, agarose, was inserted. The agarose was impregnated with chondrogenic media containing canine chondrocytes. Their data is still pending, but demonstrates yet another exciting application of 3DP in bio-scaffolds.

Additional modifications

Piezoelectricity

Piezoelectricity refers to the inherent properties of some materials to generate an electrical charge in response to mechanical stress and deformation. In terms of bone, this was first described in 1955 [58], whereby a mechanical stimulus leads to an electric one that promotes bone growth and remodeling according to Wolff's law. In fact, bone can be considered to be the archetypical piezoelectric tissue. One of the most studied conductive polymers for tissue and biomedical engineering is polypyrrole (PPy) and others include Polyaniline (PANI), poly-3,4-ethylenedioxythiophene (PEDOT), carbon nanotubes (CNTs), poly-vinylidene fluoride (PVDF) and vinylidene fluoride (VDF). They all function via inducing electrical signals to the cells via mechano-electrical transduction, i.e. once a mechanical stimulus is applied [59].

In terms of application, PVDF is the most widely used polymer in bone tissue engineering applications. In a novel experiment by Damaraju et al. [60] PVDF fibres demonstrated increased ALP activity and consequently increased mineralization of the scaffold. Unfortunately, PVDF is not degradable making implantation problematic, but it can still be used as a scaffold to culture cells pre implantation. In order to use it as an implantable scaffold, alterations will be required to make it more biodegradable.

Growth Factor Injection

There is an increasing amount of work being carried out in the stimulation of bone and cartilage growth via application of growth factors (GFs). Local delivery is preferred, as systemic delivery has additional problems related to bioavailability, short half-lives and unwanted systemic effects. In terms of GFs, several are key to bone growth and development. These include TGF-beta, BMP, IGF and FGF which all act to increase bone healing and osteoinduction [61]. VEGF is a synergistic GF, which, when combined with the others, increases osteogenesis through improving the vascularity of the bony ingrowth into a scaffold [62].

In terms of delivery, the scaffolds can be many of those discussed earlier. The scaffold will ideally contain several of these GFs with release of different factors at different times in the tissue regenerative process. Of particular advantage would be a scaffold which exhibits ideal porosity and mechanical strength as well as demonstrating piezoelectric properties married with delivery of osteoinductive GFs and VEGF. Further work still needs to be done to investigate which material will be the best to provide these attributes.

Antimicrobial Properties

Infection can be a devastating outcome in any intervention. The use of scaffolds which elute antimicrobial agents can be of dual benefit: they can help fight existing infection, similar to conventional drug eluting spacer devices, or they can be used to prevent superimposed infection in those at risk.

Although not an orthopaedic study, Sandler et al. [63] devised a model antimicrobial agent that they termed an “active pharmaceutical ingredient” (API). They used FDM type 3DP to generate their PLA models which eluted nitrofurantoin. They found 85% inhibition of biofilm formation on the nitrofurantoin eluting models relative to those without. Similar work has been demonstrated by Gu et al. [64] who used inkjet printing of antibiotics onto the surface of orthopaedic implants, resulting in reduced biofilm production.

Huang et al. [65] created a PLA polymer scaffold using FDM type 3DP. The PLA was mixed with levofloxacin powder and they constructed scaffolds from it, varying the design to alter the release of levofloxacin. They were able to establish an ideal binder solution of ethanol and acetone mix as well as demonstrate that alterations in the microstructure lead to different elution and release profiles. They compared the results from 3DP scaffolds and those via an older technique of scaffold production, conventional compression moulding. They found that 3DP led to greater accuracy and more precise microstructure which allowed them to precisely engineer levofloxacin delivery.

Conclusion

3DP is a rapidly advancing technology allowing for the unprecedented production of scaffolds for tissue engineering in orthopaedic surgery. The plethora of materials, modifications as well as the ability to create a “living implant” through integration of transplanted stem and mature cells demonstrate that this technology is the future of tissue engineering. Further work will need to focus on the optimum material, modification and cell integration for scaffold production in both trauma and elective work. This technology will become an exciting prospect in years to come.

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