Current research in development of polycaprolactone filament for 3D bioprinting: a review

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Abstract. Three-dimensional printing (3DP) provides a fast and easy fabrication process without demanding post-processing. 3D-bioprinting is a special class in 3DP. Bio-printing is the process of accurately 3DP structural design using filament. 3D bio-printing technology is still in the development stage, its application in various engineering continues to increase, such as in tissue engineering. As a forming material in 3D printing, many types of commercial filaments have been developed. Filaments can be produced from either natural or synthetic biomaterials alone, or a combination of the two as a hybrid material. The ideal filament must have precise mechanical, rheological and biological properties. Polycaprolactone (PCL) is specifically developed and optimized for bio-printing of 3D structures. PCL is a strategy in 3D printing to better control interconnectivity and porosity spatially. Structural stability and less sensitive properties environmental conditions, such as temperature, humidity, etc make PCL as an ideal material for the FDM fabrication process. In this review, we provide an in-depth discussion of current research on PCL as a filament currently used for 3D bio-printing and outline some future perspectives in their further development.

1. Introduction
Bio-printing is the process of accurately designing 3DP structures layer by layer using filaments consisting of biomaterials, cells and biomolecules [1–5]. The bio-printing process results in a fast and easy fabrication process without demanding post-processing. This technology brings an unprecedented ability to build complex, multicellular, compartmental tissue that can be used as an in vitro or implantable graft model. This technology covers several areas consisting of industrial rapid prototyping [6-7], microfluidic chips, tissue and scaffold (3D matrix/structure) engineering, prosthetics, bone replacement, bio-electronic platforms, biologically and catalytically compatible structural components [8]. In its development phase, the application of bio-printing technology continues to increase in various engineering, for example in tissue engineering (TE). TE is a scientific field that focuses mainly on the development of tissue and replacement organs by controlling biological, biophysical and biomechanical parameters in the laboratory [9]. The development of this knowledge requires an interdisciplinary research strategy that combines expertise from biology, chemistry, engineering and materials science
Figure 1. Publication trends over the past decade demonstrating a significant rise in the field of bioprinting. (a) Trends in number of publications, and (b) number of citations for articles pertaining to bioprinting [3].

Bio-printing has remained stable in its early stages of development but continues to gain popularity among generative medicine researchers because of its enormous potential in the field (Fig. 1). The steady increase in the number of publications and citations in the field of bio-printing demonstrates its enormous potential in biomedical applications including tissue engineering, drug development, and organ-on-chip platforms. While challenges exist in maintaining the desired shape and distribution of cells from construction over time, researchers have used a variety of new methods and technologies to improve the bio-printing process [10–13].

Bioprinting technology has a lot of understanding from various disciplines. In the medical world, 3D bioprinting is the automatic fabrication of multicellular networks through the spatial deposition of cells. Utilizing the concept of 3DP, which stores layers of material on top of each other, also uses biological material (material that contains living cells) as 3DP ink material, thus creating 3D-bioprinting [1–5]. 3DP is a form of additive manufacturing (AM), which is a three-dimensional object formed by adding material layer by layer. The initial step of 3DP is to create a digital model of the object to be printed. Making this digital model usually uses Computer-Assisted Design (CAD) software or uses online services that have been provided from the 3DP platform. 3D scanners can also be used to automatically create models of axial objects (such as 2D scanners). Smartphone applications can also be used to create 3D models such as Autodesk 123D Catch. 3DP can use a variety of materials both liquids and solids [14,15].

2. Filament fabrication for 3D-bioprinting
Filaments for 3D printers are mostly produced by free extrusion method. This is one of the most difficult processing techniques with extrusion, due to the impact of very large process parameters on product dimensions and material [16]. The filament is made of a thermoplastic polymer which is melted and extruded through the nozzles on the desired substrate in a layer by layer manner. Multiple or multi-extruder printing heads are often used in material extrusion systems to print multi-material components at once [17]. 3D printers use filaments as raw materials to make components. In making filaments requires an extruder machine (single or twin screw). This technology is currently developing rapidly and it is estimated that it will continue to grow. This is because this technology is able to make all forms of prototypes with various forms from accessories to the medical field.
The general filament manufacturing method is called FDM (Fused Deposition Modeling) as shown in Fig. 2. The extrusion-based molding technique was innovated by Scott Crump in late 1989 and later Stratasys Ltd. became a profit-oriented FDM machine manufacturer. Stratasys Fortus FDM printers can provide product volumes up to 915 mm$^3 \times 610$ mm$^3 \times 915$ mm$^3$ with a layer thickness equivalent to 178 µm [8, 18]. The division of filament material has been summarized by the author and [19] as shown in Table 1.

3. Polycaprolactone filament
The most commonly used polymer for 3D porous scaffold is PCL, although its cell interaction is limited due to its slightly hydrophobic nature but good biocompatibility and processability. PCL is a semicrystalline which, together with its low hydrophobicity and water absorption capacity, results in a very slow degradation kinetics, which is considered a bioresorbable material compatible with soft and hard [50]. PCL shows good cytocompatibility and promotes cell adhesion and proliferation even in the absence of cell-binding groups [3].
Table 1. Filamen non biodegradable dan biodegradable

| Matrix                  | Filler                           | Compatibilizer/Plasticizer | Toughening Agent | Dia (mm) | Ref. |
|------------------------|----------------------------------|---------------------------|------------------|----------|------|
| **Non-Biodegradable Filament** |                                  |                           |                  |          |      |
| ABS                    | Hardwood lignin + Carbon Fiber   | -                         | Nitrile Rubber   | 2,5      | [20] |
|                        | Coir Fiber                       | -                         | -                | 1,75     | [21] |
|                        | Rice Straw                       | -                         | -                | 1,75     | [22] |
|                        | Macadamia nut shell              | MAH 3% wt                 | -                | 1,75     | [23] |
| PP                     | Hemp                             | MAH-g-PP 2 % wt           | -                | 2,4-3,1  | [24] |
|                        | harakake                         | MAH-g-PP 2 % wt           | -                | 2,4-3,1  | [24] |
|                        | Hemp                             | MAH-g-PP 2 % wt           | -                | 3        | [25] |
|                        | Gypsum                           | MAH-g-PP 2 % wt           | -                | 3        | [25] |
| Bio-PE                 | TMP                              | MAH-PE                    | -                | 2        | [26] |
|                        | TMP                              | MAH-PE                    | -                | 2        | [27] |
| TPU                    | Poplar Wood Flour                | EPDM-g-MAH, POE-g-MAH, kitsosan, MDI 5% | - | 1,75 | [28] |
| **Biodegradable Filament** |                                  |                           |                  |          |      |
| PLA                    | Paulawnia wood                   | -                         | -                | 1,75     | [29] |
|                        | Orange wood                      | -                         | -                | 1,75     | [29] |
|                        | Aspen sawdus                     | -                         | -                | 1,75     | [30] |
|                        | Bamboo                           | -                         | PEG600, Ester Gliserol, Tributyl citrate | 1,75     | [31] |
|                        | Poplar Wood                      | -                         | -                | 1,75     | [32] |
|                        | Sawdust                          | -                         | -                | 1,75     | [33,34] |
|                        | Pine Lignin                      | -                         | -                | 1,75     | [35] |
|                        | Poplar wood                      | Graft kopolimer glycidyl methacrylate, Dicumyl Peroxide/Aliphatic polyester 10% wt Tributyl citrate 5%wt | TPU,POE 10% wt | - | [36] |
|                        | Cork Powder                      | cPLA1–cPLA2               | -                | 2,85     | [38] |
|                        | TMP                              | -                         | -                | 2,2      | [39] |
|                        | Poplar wood                      | -                         | POE              | 1,75     | [40] |
|                        | Sugarcane                        | -                         | -                | 1,75     | [41] |
|                        | Harekeke                         | -                         | -                | -        | [42] |
| PHB                    | Sawmill                          | -                         | -                | 1,75     | [43] |
| PCL                    | Cocoa Shell                      | -                         | -                | 1,75     | [44] |
|                        | Gum rosin                        | -                         | -                | 2,8–3    | [45] |
|                        | Beeswax                          | -                         | -                | 2,8–3    | [45] |
|                        | Sodium Alginate                  | -                         | -                | 1,3      | [46] |
|                        | Indomethacine                    | PEG 10% wt, ARA           | -                | 1,78-1,83| [47] |
|                        | Corn starch                      | -                         | -                | 1,75     | [48] |
|                        | Potato Starch                    | -                         | -                | 1,75     | [48] |
| PLA+PHA                | Cellulose pulp                   | -                         | -                | 1,75-3   | [49] |

Many researchers have started to introduce the polymer into a 3D printing strategy to better control the interconnectivity and porosity of PCL [3,52-53]. Compared to other commercially available
bioresorbable polymers, PCL is one of the most flexible and easy to process materials. Its structural stability and properties that are less sensitive to environmental conditions, such as temperature, humidity, etc. make PCL an ideal material for the FDM fabrication process[8].

Table 2. Review of PCL-based 3D application studies

| Ref.  | Blending Component                                  | Methods                                                                 | Analysis                                                                 |
|-------|-----------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|
| [45]  | PCL-GR-BW                                           | mixing using co-rotating twin-screw extruder                           | Printability Tests & Rheology, DSC, Tensile test, DMTA, FTIR, SEM, contact angle measurements, wettability and colour |
| [46]  | PCL-SA                                              | Manual blending and casting in petri dishes & heat extruder             | SEM, EDX, DSC, Mechanical properties, & UV-Vis                           |
| [48]  | PCL-corn starch, potato starch, soluble starch      | mixing using single & twin-screw extruder                              | 3D-printability, tensile strength, rheological properties, crystallization properties & biological performance |
| [54]  | PCL/PLA blend                                       | Extrusion &Fused Filament Fabrication (FFF)                            | Printability test & ANOVA                                               |
| [55]  | PCL                                                | mixing using magnetic stirrer & combined extrusion-based cryogenic 3D printing | Accelerated alkaline degradation, SEM, Tensile, Porosity, biocompatibility, ANOVA |
| [56]  | PCL-HA                                              | Technic of wire-network molding (WNM)                                  | Porositas, Cell proliferation and viability assays, & ANOVA             |
| [57]  | PCL/PLA blend                                       | Melt blending                                                          | Thermography characterisation, TGA, SEM, tensile, compression, biological test |

PCL has been developed as a filament modeling material to produce a porous scaffold, made of parallel microfilament layers, using computer-controlled extrusion and deposition processes[51]. PCL scaffolds are produced with a channel size range of 160–700 mm, filament diameter of 260–370 mm, and porosity of 48–77% and regular geometric honeycomb pores depending on processing parameters. The different porosity of the frame also shows the characteristic pattern of stress-strain behavior of the porous solid under the load. The compressive stiffness ranges from 4-77MPa, strength 0.4-3.6 MPa, and stretches from 4 to 28%. The analysis of the measured data showed a high correlation between the porosity of the frame and the compressive properties based on the energy law relationship [51].

In the process, the monofilament is driven by two rollers and acts as a piston to drive the semi-liquid extrudate. At the end of each finished layer, the base platform is lowered and the next layer is stored. The designed object is created as a 3D piece based solely on the proper deposition of the extrudate thick layer. The path and deposition parameters for each layer are determined depending on the material used, fabrication conditions, application of the part being designed and the preferences of the designer as shown in Fig.3 [51]. According to [58], PCL is one of the less popular polymers in the 3DP community but its filament which is the best and still has its practical uses as well as the development of training accessories for sports. This filament is a durable material that provides flexible strength and size.
4. Conclusion
This paper discusses the current research in development PCL filament for recent trends in 3D-bioprinting. 3D-bioprinting technology utilizing PCL filaments has entered a very promising research development stage. PCL is a strategy in 3D printing to better control interconnectivity and porosity spatially. PCL is one of the most flexible and easy to process materials. Structural stability and less sensitive properties environmental conditions, such as temperature, humidity, etc make PCL as an ideal material for the FDM fabrication process. The various advantages of these biodegradable resins are a new challenge for researchers to develop research towards mixing PCL with various hybrid materials.

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