Hydrogels as Bioinks for 3D bioprinting: Properties and Application

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Introduction
The rise of 3D-printing commenced in the early 1980s, when 3D-printing pioneer Chuck W. Hull invented the first stereolithographic manufacturing method. Today, additive manufacturing techniques are applied in many different fields ranging from rapid tooling to mechanical engineering, education, art and over to biomedicine. Especially the latter is of high research interest, since 3D-bioprinting enables scientists to perform 3D cell experiments under more sophisticated circumstances, than the ones possible with conventional cell culture. With bioprinters, such as the pneumatic microextrusion Biobot 1 (Fig. 1), cell laden biomaterials can be processed with precision to bioengineer tissue three dimensionally. Bioprinting development relies on recent advances in 3D-printing technology, cell biology and material sciences and enables the production of functional tissue units in vitro.

Here, we present two different bioinks, a gelatin methacryloyl bioink, supplemented with hyaluronic acid (GelMAHyA), and an alginate bioink in a novel crosslinking technique for bioprinting.

Bioprinting and Bioinks
Appropriate bioinks for bioprinting should fulfill following requirements: (1) appropriate viscosity and shear-thinning properties, (2) quick crosslinking, (3) stability over prolonged cultivation under physiological conditions and (4) biocompatibility.

Hydrogels are water-retaining insoluble polymers which are already applied in 3D mammalian cell culture. Some hydrogels of natural origin as proteins and carbohydrates display high biocompatibility and allow cell remodeling, attachment and spreading. Ideally, a quick and controlled sol-gel transition, through a change in temperature or pH, allows printing with high precision and resolution. Some hydrogels do not possess such properties and must be chemically modified to allow fast curing during printing.

Gelatin methacryloyl, supplemented with hyaluronic acid (GelMAHyA)
Gelatin provides RGD-sequences for cell attachment and can also be remodeled by metallo-proteases produced by cells. Chemical linking of methacrylic anhydride to the gelatin produces a thermally and photo inducible polymer which forms a stable hydrogel (Fig. 2 and 3). Adding the connective tissue polysaccharide hyaluronic acid and gelatin improves unpolymerized gel viscosity and increases unpolymerized gel viscosity and improves printing behavior by avoiding material leakage before and during printing process. In addition, it promotes post-print material stability and cell migration.

Sodium alginate bioprinting in CaCl₂ vapor
Sodium alginate is polymerized by ionic crosslinks with CaCl₂ and has already been extensively used as a bioink. Normally, in order to convert the liquid alginate to a gel, the bioink is printed directly into a CaCl₂ solution. We have developed a novel crosslinking approach using a customized 3D-printed vaporizer. This method allows the decrease of possible toxic effects of CaCl₂ on cells and improves printed construct grip to the culture plate surface, as well as interlayer adhesion. The vaporization chamber (LR05) was designed using Autodesk Inventor Professional CAD software and printed with an 3D Systems multi jet printer. The LR05 was designed to provide high vapor density without affecting the bioprinting process.