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Review

Printing technologies for biomolecule and cell-based applications

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ABSTRACT

Biomolecules, such as enzymes, proteins and other biomacromolecules (polynucleotides, polypeptides, polysaccharides and DNA) that are immobilized on solid surfaces are relevant to many areas of science and technology. These functionalized surfaces have applications in biosensors, chromatography, diagnostic immunoassays, cell culturing, DNA microarrays and other analytical techniques. Printing technologies offer opportunities in this context. The main interests in printing biomolecules are in immobilizing them on surfaces for sensors and catalysts or for controlled delivery of protein-based drugs. Recently, there have been significant developments in the use of inkjet printing for dispensing of proteins, biomacromolecules and cells. This review discusses the use of roll-to-roll and inkjet printing technologies in manufacturing of biomolecule and cell-based applications.

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1. Introduction

Smaller biomolecules, such as enzymes, proteins and other biomacromolecules (polynucleotides, polypeptides, polysaccharides and DNA) immobilized on solid surfaces are relevant to many areas of science and technology, finding applications in biosensors, chromatography, diagnostic immunoassays, cell culturing, DNA microarrays and other analytical procedures (Hermanson et al., 1992). Various high throughput methods such as inkjet printing (Delaney et al., 2009) and roll-to-roll printing methods such as flexographic printing (Phillips et al., 2012), microcontact printing (Austin and Holway, 2011; Bernard et al., 1998, 2000), capillary drop patterning (Delehanty, 2004) and spot and line deposition (Kang et al., 2012) have been utilized for biomolecule deposition on a range of surfaces, such as glass slides, nitrocellulose coated slides, plastics, paper and polymeric membranes. Different printing techniques that are of potential interest in biomolecule printing are illustrated in the Fig. 1.

The main interests in printing proteins are in immobilizing them on surfaces for sensors and catalysts or for controlled delivery of protein-based drugs (Hutchings and Martin, 2012). In addition, the utilization of printing technologies for pattering proteins for the roll-to-roll manufacturing of biomolecule arrays is driven by the desire to miniaturize processes in order to achieve cost efficiency. Recently there have been significant developments in the use of inkjet printing for dispensing of proteins and

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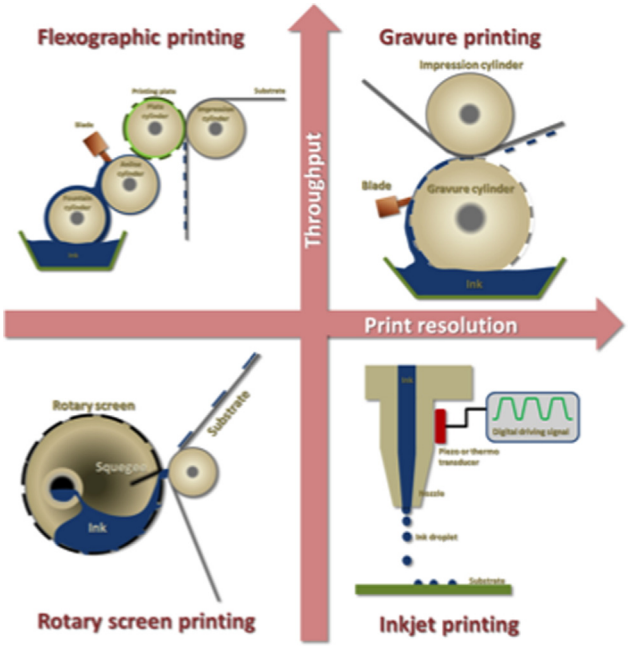

Fig. 1. Schematic presentation of printing technologies that are of potential interest for biomolecule printing. The printing technologies are qualitatively divided according to their print resolution and throughput capabilities.

biomacromolecules. The adaptation of inkjet printing technology to the complex fields of tissue engineering and biomaterial development presents potential to increase progress in these emerging technologies through the implementation of this high-throughput capability via automated processes to enable precise control and repeatability.

There are many unique applications in diagnostics and drug discovery that can potentially be utilized with printing technologies, including high-throughput screening, genomics and combinatorial chemistry (Saunders et al., 2008). In high-throughput screening, higher density, lower volume assay plates are being investigated because of the combined effect of decreased reagent/consumable use and increase throughput (more assays per plate). There are several application areas in high-throughput screening that utilize pico to nanoliter dispensing. For example, the bulk dispensing of reagents and components where the high density, low volume assay is performed in a microwell plate containing the compound of interest and requires reagents to be added to all wells at the same concentration and volume. Other application areas include compound reformatting, where the compounds are transferred from one plate source into another, higher density plate. Additional application areas are pre-prepared direct assay plates and direct preparation of dose-response curves. Rather than performing off-line serial dilutions to achieve the concentration range sufficient to perform a dose-response study (4–6 orders of magnitude of dilution), inkjet dispensing systems can be used to perform serial dispenses. In this operation, increasingly larger volumes are added to successive wells, in situ, to cover the sufficient concentration range. Fig. 2 shows a schematic presentation of the application of roll-to-roll fabricated printed paper-based 2D reaction array platform that can be used e.g., for screening assays and for which dispensing can for instance be made with inkjet printing technology (Juvonen et al., 2013).

Basic application areas involve dispensing DNA onto substrates (membranes, glass slides, silicon wafers, etc.,) and probing for complementary base-pair binding. The detection mode is usually radiometric or photometric (e.g., fluorescence). The DNA molecules are typically contained in microarray formats so the process is similar to that outlined above**.** The challenges in miniaturizing (bio)chemical synthesis are significant. For example, automation equipment needs to be chemically compatible with a wide range of solvents, many which are corrosive to the normal engineering materials in instrumentation. Inkjet dispensing technology holds considerable promise as a liquid handling technique capable of addressing the projected needs for miniaturization, as it has the potential to deliver small volumes of reagents with high speed. A combination suitable printing techniques and suitable substrate properties opens up many opportunities in fabrication of biomolecule and cell-based systems. This review demonstrates and discusses the use of roll-to-roll and inkjet printing technologies in manufacturing of biomolecule and cell-based applications

2. Ink development for biomolecules

In order to deliver biomolecules by printing, a suitable ink has to be developed. These bioinks will normally be aqueous buffer solutions containing salts, other small solutes, and biomolecules. In addition, humectants such as ethylene glycol or glycerol are added to prevent the ink to dry in the nozzles. In the ink development, two major parameters, which should be considered, are viscosity and surface tension. The operational window in terms of rheological properties depends on the selected printing method. For example, inkjet printers will normally function over a viscosity range from 1 to 20 mPa s and a surface tension range from 25 to 60 mN/m (Hutchings and Martin, 2012). The increase in viscosity will decrease the speed and accuracy of the expelled drop and the printing will fail at high viscosities and high drop rates if the ink cannot flow into the liquid chamber rapidly enough to refill it

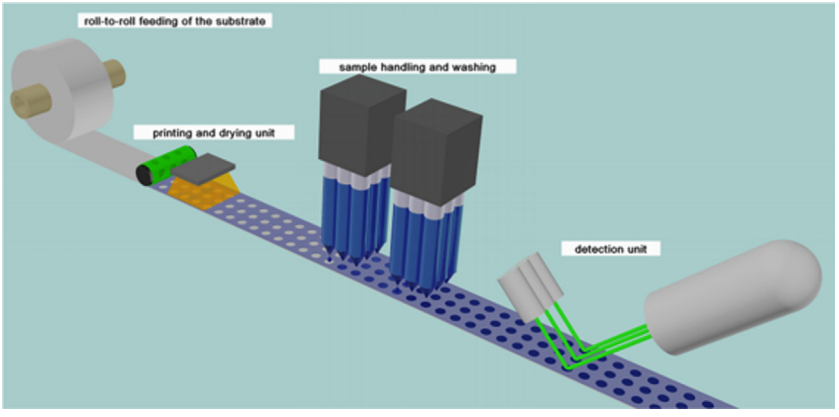

Fig. 2. Schematic presentation of the application of roll-to-roll fabricated printed paper-based 2D reaction array platform for high-throughput biomolecule screening assays.

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