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Review

Drawing lithography for microneedles: A review of fundamentals and biomedical applications

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ABSTRACT

A microneedle is a three-dimensional (3D) micromechanical structure and has been in the spotlight recently as a drug delivery system (DDS). Because a microneedle delivers the target drug after penetrating the skin barrier, the therapeutic effects of microneedles proceed from its 3D structural geometry. Various types of microneedles have been fabricated using subtractive micromanufacturing methods which are based on the inherently planar two-dimensional (2D) geometries. However, traditional subtractive processes are limited for flexible structural microneedles and makes functional biomedical applications for efficient drug delivery difficult. The authors of the present study propose drawing lithography as a unique additive process for the fabrication of a microneedle directly from 2D planar substrates, thus overcoming a subtractive process shortcoming. The present article provides the first overview of the principal drawing lithography technology: fundamentals and biomedical applications. The continuous drawing technique for an ultrahigh-aspect ratio (UHAR) hollow microneedle, stepwise controlled drawing technique for a dissolving microneedle, and drawing technique with antidromic isolation for a hybrid electro-microneedle (HEM) are reviewed, and efficient biomedical applications by drawing lithography-mediated microneedles as an innovative drug and gene delivery system are described. Drawing lithography herein can provide a great breakthrough in the development of materials science and biotechnology.

1. General introduction

In recent years, as various biological drugs (e.g. proteins, vaccines, DNA, antibodies and genes) have been developed by advances in biotechnology, DDSs have focused on efficient and safe administration of the drugs [1,2]. However, conventional DDSs such as oral inoculation and hyperdermic injection are not suitable in the issues of efficiency and safety due to the low oral bioavailability of biological drugs and pain caused by a needle, respectively. Thus, percutaneous drug administrations have been evaluated as an alternative approach with easy accessibility, safety, and patient-friendliness based on self-administration [3–5]. The skin barrier, nevertheless, is impermeable to general biomolecules which generally have hydrophilicity, and macro-size (over 500 Da) and novel DDSs to overcome the impermeable skin barrier are required [6,7]. The progress of material science allows for the possibility to develop new physical and chemical DDSs that improve the efficacy of drugs by overcoming the skin barrier [8,9].

A microneedle, a 3D material with external micro-scale dimensions, has been introduced as a microporation-mediated physical DDS for percutaneous drug administration; a microneedle can produce superficial pores in the skin by disruptions of the stratum corneum, and the pore routes allow local permeation of a drug into the skin [10–12]. The remarkable function of microneedles in biomedical applications is derived from the 3D structure which can penetrate the skin barrier with a minimally invasive manner thus making self-administration patient-friendly [12,13]. The injection of liquid drug formulation, innocuous release of an encapsulated drug and intracellular transfection of a gene can be achieved by microneedles which can be classified as hollow microneedles, dissolving microneedles and integrated microneedles with an electrode.

Subtractive process, a widespread manufacturing tool for the production of a 3D microstructure, was introduced to fabricate microneedles, in which the shape of a microneedle was selectively carved out of a 2D substrate's planar geometry [13,14]. Although several drugs have been successfully delivered using traditional subtractive process-mediated microneedles, the restricted microneedle designs were difficult for creating a functional microneedle which showed flexible biomedical applications: high-aspect ratio

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for intradermal liquid drug injection, stable encapsulation of a drug for transdermal innocuous release and monolithic assembly of a microneedle with an electrode for percutaneous gene transfer. One method to surpass the limitations of the subtractive process suggests an additive process-based innovative microfabrication, which can design flexible microneedles for the demands of biomedical applications as efficient DDSs.

The present article reviews drawing lithography as a unique additive process to fabricate microneedles, in which a 3D polymer structure is directly extended from 2D viscous polymer materials, thus overcoming the drawbacks of the subtractive process. The authors suggested the first drawing lithography for manufacturing microneedles, and have developed various drawing techniques for flexible microneedle implementations [15–17]. The present review is the first attempt to clarify the overall drawing lithography. How to create 3D microneedle structures using drawing lithography, as well as the parameters for fabrication of a microneedle in a drawing lithography model will be introduced. Subsequently, the paper provides flexible drawing techniques to design 3 types of microneedles: continuous drawing for an UHAR hollow microneedle, stepwise controlled drawing for a dissolving microneedle and drawing with antidromic isolation for a HEM. Moreover, results of percutaneous drug and gene administration in a biomedical application using drawing lithography-mediated microneedles are described.

2. Background of drawing lithography

2.1. Onset of drawing lithography: the glass transition of a polymer

In drawing lithography, understanding of the glass transition of a polymer is critical to fabricate a microneedle, because drawing lithography uses the viscous property of a polymer in the glass transition as a key parameter to realize the manufacturing performance of a 3D microstructure. The glass transition is a kinetic process between a solid state and liquid state of any amorphous portion of the polymer material, and is exponible by the glass transition temperature (T_g), which is most closely related to the state of thermal molecular motion [18,19]. When a melted liquid polymer cools down to T_g, the amorphous portion of the polymer gradually becomes a more viscous glassy liquid (glass-forming liquid) with a Newtonian fluid-like response, because thermal molecular motions decrease. As temperature decreases below T_g, the glassy liquid turns into a solid state because of the structural rearrangements with little relative mobility [20]. Thus, the glass transition is different from a well-defined general phase alteration [21,22], and viscosity is an important parameter to describe the kinetic process when a melt is under cooled from the melting point (T_m) to T_g [23].

The viscosity is determined by the rate of molecules moving from 1 equilibrium position to another in elastic models of glassy liquids [24], and the temperature dependence of viscosity is a remarkable feature in glass transition [25,26]. As shown in the Angell plot of Fig. 1A, close to T_g the shear viscosity (η_S) of a few strong liquids such as pure silica (SiO_2) and germanium dioxide (GeO_2) logarithmically increases with temperature and is well described by the Arrhenius functionality, $\eta_S \sim \exp(\Delta E/kT)$, where ΔE is temperature-independent as the activation energy and k is Boltzmann's constant [27]. In the vast majority of cases however, viscous liquids as fragile liquids represent a stronger than Arrhenius increase of the shear viscosity upon cooling close to the glass transition (Fig. 1B), and this super-Arrhenius behavior is fitted by the Vogel–Fulcher–Tammann (VFT) Eq. (1), where A is the temperature-independent constant, and T_0 is the ideal T_g [28–30].

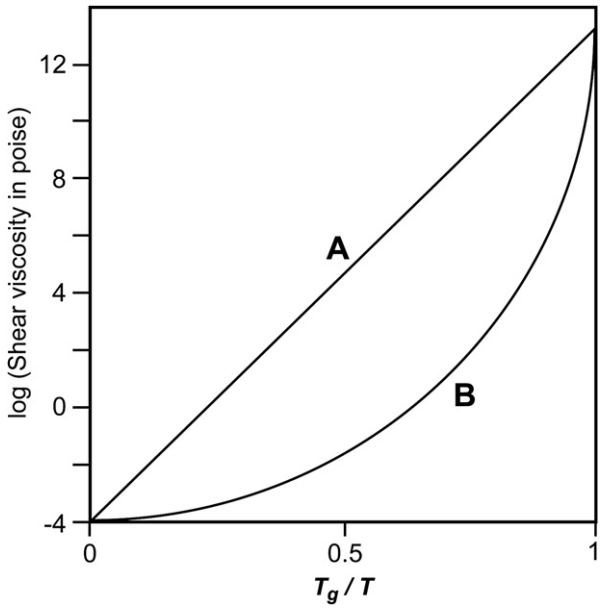

Fig. 1. The Angell plot represents a significant increase of viscosity as a function of inverse temperature normalized to 1 at T_g. (A) Arrhenius behavior of strong liquids. (B) Super-Arrhenius behavior of fragile liquids.

$$\eta_S \sim \exp[A/(T - T_0)] \tag{1}$$

Eq. (1) implies as a glassy liquid polymer approaches its T_0, there is an exponential increase in shear viscosity [31]. Thus, a significant increase of shear viscosity in the glass transition is observed as the onset point of drawing lithography, and especially, the processability parameter (P, or stringiness) directly depends on shear viscosity as shown in Eq. (2), where σ is surface tension, and h_m is the solvent mass transfer-coefficient [32].

$$\text{Processability parameter } (P) = \frac{\eta_S}{\sigma} h_m \tag{2}$$

In the glass transition, the viscous polymer has processability for drawing lithography. Additionally, the extensional viscosity (η_E) is another parameter for extensional deformations in drawing lithography, and the initial planar extensional viscosity (η_{iE}) as an elasticity parameter in glass transition shows exponential increase as temperature dependence due to the Trouton's rule [33].

$$\text{Trouton ratio } (\text{Tr}) = \eta_{iE}/\eta_S = 3 \tag{3}$$

2.2. Drawing lithography model

2.2.1. Drawing lithography: extensional deformation

Drawing lithography is characterized by an elastic deformation of polymer materials in the glassy transition, and the 3D microneedle structures were fabricated from viscous polymers by extensional deformation (stretching deformation). Initially, a glassy liquid, which has viscosity and processability, was placed between 2 identical circular plates. As the concentric rigid plate contacted the glassy liquid, a liquid-plate interfacial adhesion was initiated. Subsequently, the glassy liquid was elongated by pulling of a plate, and in the extensional deformation apparatus, a liquid structure was first generated between 2 circular plates. In the instantaneous length at uniform deformation of Fig. 2, the Hencky strain (ε) can be expressed by Eq. (4).