Bioactive Materials 3 (2018) 434–445

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: http://www.keaipublishing.com/biomat

Polymeric biomaterials for biophotonic applications

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ARTICLE INFO

Keywords:
Biophotonics
Biomaterials
Imaging
Sensing
Phototherapy

ABSTRACT

With the growing importance of optical techniques in medical diagnosis and treatment, there exists a pressing need to develop and optimize materials platform for biophotonic applications. Particularly, the design of biocompatible and biodegradable materials with desired optical, mechanical, chemical, and biological properties is required to enable clinically relevant biophotonic devices for translating *in vitro* optical techniques into *in situ* and *in vivo* use. This technological trend propels the development of natural and synthetic polymeric biomaterials to replace traditional brittle, nondegradable silica glass based optical materials. In this review, we present an overview of the advances in polymeric optical material development, optical device design and fabrication techniques, and the accompanying applications to imaging, sensing and phototherapy.

1. Introduction

The swelling demand for higher quality healthcare and disease treatments has drawn considerable attention to biophotonics, which integrates optical techniques into the fields of biology and medicine to enable new imaging, sensing, and therapeutic strategies. The development of biophotonic technology promotes the progress of early detection and diagnosis of diseases, new modalities of light-guided and light-activated therapies, as well as increased understanding of biological systems [1]. Specifically, optical bioimaging, which forms a major thrust of biophotonics, provides non-invasive, high-sensitivity and high-resolution macroscopic information of a wide range of biological specimens (from cells to tissues), realizing effective and affordable diagnosis of various diseases including cervical cancer, oral cancer, and epithelial cancer [2–5]. Optical biosensing is another widely studied biophotonic application for chemical identification and disease diagnosis. Optical biosensors utilize optical responses (intensity, wavelength, or polarization variations) created by chemical or biological changes to indicate a physiological disorder or problem. The sensitivity and selectivity of the optical responses are strongly dependent on the functionalization of biorecognition elements on an optical device, such as an optical waveguide or an interface supporting surface plasmonic resonance [2,6]. With the development of optical biosensors, real-time, remote, and multiplexed sensing can be achieved within a single device. In fact, many optical biosensors have been involved in applications for detecting biomarkers of various cancers including breast cancer, lung cancer, melanoma cancer and lymphoma cancer [7–9], as well as diseases such as celiac disease and Alzheimer's disease [10–12]. Additionally, biophotonics promotes the development of light-activated therapy that has emerged as a promising treatment of many medical problems. For example, photodynamic therapy (PDT) [2,13], which utilizes photosensitizing agents along with light to kill tumor tissues, bacteria, fungi and viruses, has been applied as a non-invasive treatment for diseases such as endodontic disease [14], and cancers such as skin cancer [15], breast cancer [16], leukemia cancer [17], as well as head and neck cancer [18]. Indeed, biophotonics has been so effective in its aims that it is being hailed as one of the most promising technologies in biomedical fields.

To achieve the full potential of biophotonic technology, the availability of suitable optical materials is of crucial importance, as their optical properties, mechanical properties, chemical structures, and biological functionalities significantly affect the device performance [19,20]. A fundamental requirement for suitable optical materials is the capability to achieve high-efficiency light delivery with low loss. To

Peer review under responsibility of KeAi Communications Co., Ltd.

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https://doi.org/10.1016/j.bioactmat.2018.07.001
Received 6 April 2018; Received in revised form 26 July 2018; Accepted 28 July 2018

date, silica glass remains the mainstream optical material platform. Silica-based materials possess excellent optical properties, including high transparency over a broad spectral range from the visible to the near infrared (NIR) wavelengths, allowing them to be adopted in a wide variety of applications including optical sensors [21]. However, silica glass is a poor match for many biological applications as the material's mechanical fragility and brittleness are an injury risk to biological tissues. Additionally, biological applications require materials with improved biocompatibility and biological functionalities, which are challenging to realize with traditional silica material. Nondegradability is another significant hindrance for *in vivo* usage of silica-based optical devices, as implantable medical devices ideally should be degraded and cleared following their use, leading to a pressing need for biodegradable optical materials to replace silica. Therefore, the development of novel biocompatible polymeric materials with flexible mechanics, high optical efficiency, adjustable degradation, and design versatility are required to realize the full potential of biophotonics and create the next generation of optical sensing, imaging, and treatment technologies [22–25].

Benefiting from the recent progress of polymeric biomaterials, many biophotonic devices with desired properties and functionalities for various medical applications have been developed with advanced polymeric biomaterials. Nature-inspired optical systems based on biological components such as bacterias [26–28], have been demonstrated; however, these systems suffer from limited sources, restrictive designability, and inherent variability. Such limitations have led to the development of natural [29–35] or synthetic polymer [25,36,37] based optical materials, which have more design flexibility to enable versatile physical, chemical, or biological properties and functionalities. In this review, we discuss the various families of biomaterials, including bacteria cell-based biomaterials, naturally derived biomaterials, and synthetic biomaterials, in the field of biophotonics (Table 1). Their material properties, fabrication strategies, functionalities and applications (in particular, optical probing, diagnostics, and light-activated therapies) are described. We aim to provide systematic understanding of the development of optical biomaterials, their critical requirements, and an outlook on future directions.

2. Properties of polymeric optical biomaterials

For the applications of biophotonics including optical imaging, optical sensing, and light activated therapy, optical materials are required to fabricate optical elements such as waveguides (a physical structure that guides electromagnetic waves in the optical spectrum) and lenses (optical components designed to focus or diverge light) to transmit, detect and transform light. Optical materials can be defined as materials with the function to control or alter electromagnetic radiation in the ultraviolet (UV), visible, and infrared (IR) spectral regions. For biophotonics applications, materials need to meet certain optical, mechanical, chemical, and biological properties [38].

In the choice of an optical material, the most important properties are often the degree of transparency and the refractive index, along with their spectral dependency [39]. Materials with high transparency have relatively low reflection, absorption, and scattering of light, which together result in low optical loss. For silica fibers, atomic structural imperfections can cause light scattering (Rayleigh scattering) [40], which decreases with increasing wavelength. With technical advances in glass purification, glass manufacturing, and application of long-wavelength light around 1550 nm, silica fibers with low optical loss (~ 0.2 dB/km) are widely applied and popular for long-haul fiber-optic communication. Polymeric biomaterials, which refer to polymers that have been engineered to interact with biological systems for therapeutic or diagnostic purposes, usually have inhomogeneity arise from a partially disordered network of polymer chains and macromolecules. The sizes of the inhomogeneity extend to tens of nanometers to micron scales rather than the atomic scale. Mie-type light scattering [41], which can be several orders of magnitude stronger than Rayleigh scattering, occurs when the inhomogeneity size scale is greater than about one tenth of optical wavelength. In addition, organic molecules usually have strong absorption at short wavelengths below 350–400 nm, while some conjugated structures can have absorption peak in the visible spectrum, so generally conjugated polymeric biomaterials are not considered for optical device applications. Commonly developed transparent polymeric biomaterials have an optical loss in the range of 0.3–1 dB/cm, which is much higher than that of silica glass. Despite the relatively higher optical loss, polymeric optical biomaterials can still meet the distance of interest (usually less than 1 m) in most biomedical applications. The refractive index of a material, defined as the ratio of speed of light in vacuum to the phase velocity of light in a material or a medium, also affects material optical loss. For single-material waveguides, the refractive index of the material should be higher than that of the surrounding tissue (1.38–1.41 at visible

Table 1
Summary of polymeric biomaterials for biophotonic applications.

Type		Examples	Pros	Cons	Applications
Living biomaterials		*E. coli*, Cyanobacteria,	Superior biocompatiblity	Small size, Limited modification methods, Strict process condition	Waveguide [26–28]
Naturally derived polymers		DNA, Silk, Chitosan, Cellulose, Agarose	Biocompatibility, Biodegradability	Property variability, Limited sources, Poor designability	Waveguide [31,34,36,53], Optical fiber [35,42], Biosensor [44,46-52]
Synthetic polymers	Non-degradable polymers	Polyethylene glycol (PEG), Polyacrylamide (PAM), Polydimethylsiloxane (PDMS)	Flexible designability	Non-degradability	Waveguide [57], Optical fiber [37], Biosensor [55,56,58,59], Optogenetic therapy [25]
	Biodegradable polymers	Poly (lactic acid) (PLA), Poly (lactic-co-glycolic acid) (PLGA), Citrate-based Biomaterials	Flexible designability, Biodegradability		Waveguide [65], Optical fiber [24], Biosensor [67], Microneedle array [66], Biomaterial laser [67,68], Phototherapy [65,66]
Combinations of Materials		PEG/alginate, Alginate/PAM, P (AM-co-PEGDA)/alginate	Flexible designability		Waveguide, Optical fiber [79], Biosensor [80,81], Phototherapy [79], Light amplification [79]