

use of silk dates back to its use as a suture material; here the unique physical properties, handling and biocompatibility of silk fibres have been critical for its continued success, as well as for its approval by the Food and Drug Administration (FDA) as a biopolymer for use in humans. However, the medical applications of silk that have emerged over the past decade go beyond its traditional load-bearing applications (Altman et al. 2003; Omenetto and Kaplan 2010). In this chapter, we examine the role of silk in drug and cell delivery applications, with specific reference to silk hydrogels, and we highlight emerging trends, opportunities and challenges, as well as provide a sound background on silk biopolymers for the silk novice.

Silk Structure-Function Relationships

For the purpose of this chapter, we use the term silk to refer to protein-based fibre-forming materials spun by living organisms. Spiders and silkworms are the most prominent organisms associated with silk production, although silks are made by many arthropod taxa (Vollrath and Porter 2009; Porter et al. 2013). Furthermore, spiders make more than one type of silk. For example, the common European garden spider, *Araneus diadematus*, and the golden silk spider, *Nephila clavipes*, spin seven different silks from seven sets of different silk glands (Vollrath 1992); these silks are often used in combination simultaneously to fine tune the overall fibre composition and subsequent performance. Nonetheless, the silks used for drug delivery applications are typically those produced by the silkworm, *Bombyx mori*, or recombinant versions of spider silks (Yucel et al. 2014). Where appropriate, we distinguish between silkworm silk (fibroin) from the cocoons of *B. mori* and spider silks. We also differentiate silk materials that are reverse engineered native proteins from those generated in heterologous hosts via genetic engineering. When not specifically stated, we refer to silkworm silk because *B. mori* silk is most commonly used due to its abundance (Seib and Kaplan 2013). The hierarchical structure of silk enables this biopolymer to serve specific functions (Fig. 1a,b), including tailored drug release and payload protection. The following section details silk structure with specific reference to drug delivery.

Bombyx mori Silk

The *B. mori* silk heavy chain consists predominantly of five amino acids: 45.9% glycine (G), 30.3% alanine (A), 12.1% serine (S), 5.3% tyrosine (Y), and 1.8% valine (V) and only 4.6% of the other 15 amino acid types (Zhou et al. 2001). *B. mori* silk is a very large (2.3 MDa) protein that is made up of a heavy chain (approximately 350 kDa) (Zhou et al. 2000) and a light chain (approximately 26 kDa) (Yamaguchi et al. 1989) that are held together by a single disulphide bond at the C terminus (Tanaka et al. 1999) (Fig. 1b); this disulphide linkage is critically important for the successful secretion of silk from the silk gland. The 2.3 MDa elementary silk unit is composed of six sets of disulphide-linked heavy and light chain heterodimers that assemble and are physically complexed by one molecule of fibrohexamerin (P25, approximately 25 kDa). Fibrohexamerin has *N*-linked high mannose type oligosaccharide chains that facilitate the physical interaction with the silk heavy chain (Inoue et al. 2000; Inoue et al. 2004). The 6:6:1 molar ratio of heavy chain, light chain and fibrohexamerin that makes up