REVIEW ON FABRICATION AND APPLICATION OF REGENERATED *BOMBYX MORI* SILK FIBROIN MATERIALS

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Abstract:

Natural silk fiber derived from the *Bombyx mori* (*B. mori*) silkworm has long been used as a luxury raw material in textile industry because of its shimmering appearance and durability, and as surgical suture for its high strength and flexibility. Regenerated silk fibroin, as the main protein extracted from the cocoons of the *B. mori* silkworm, recently has gained considerable attention due to its outstanding properties, including facile processability, superior biocompatibility, controllable biodegradation, and versatile functionalization. Tremendous effort has been made to fabricate silk fibroin into various promising materials with controlled structural and functional characteristics for advanced utilities in a multitude of biomedical applications, flexible optics, electronics devices, and filtration systems. Herein, reverse engineered silk fibroin extraction methods are reviewed, recent advances in extraction techniques are discussed. Fabrication methods of silk fibroin materials in various formats are also addressed in detail; in particular, progress in new fabrication technologies is presented. Attractive applications of silk fibroin-based materials are then summarized and highlighted. The challenges faced by current approaches in production of silk fibroin-based materials and future directions acquired for pushing these favorable materials further toward above mentioned applications are further elaborated.

Keywords:

B. mori silk fibroin; biocompatibility; biodegradation; biomedical application; flexible optics; electronics devices; filtration

1. Introduction

In addition to polysaccharides, lignin, natural rubber, and natural polyesters, silk of the proteins class is another kind of abundant naturally derived polymer produced through the secretion “spinning” process by a number of arthropod lineages (Figure 1a). For different sources and biological functions, the silk composition, structure, and properties may differ significantly [1]. Among silk variants, silk derived from the silkworm *Bombyx mori* (*B. mori*) is the most popular, characterized, and commercially used silk due to its large-scale availability, reproducibility, and desirable properties (Figure 1b). *B. mori* silk has historically been considered as the queen of textiles because of its unique shimmering appearance, tactile properties, durability, dyeability, excellent mechanical strength, flexibility, breathability, and comfort it provides in warm or cold weather, and it has long been used as a luxury raw material in the textile industry. In addition, it has also been used for surgical sutures since ancient times due to its biocompatibility, biodegradability, and non-immunogenicity. Nowadays, silk sutures are used primarily for eye and lip surgery, intraoral surgery, and some skin wounds, mainly because of their excellent handling and tying capabilities [2, 3].

B. mori silk possesses a core-shell structure comprising a silk fibroin filament core coated with glue-like sericin. Generally, the percentage of silk fibroin protein is about 70–80%, silk sericin accounts around 20%–30%, followed by small amounts of other impurities, in one silk thread (Figure 1c) [4]. Silk fibroins are composed of bundles of nanofibrils, which are oriented parallel to the axis of the filaments. The strong interaction between the twisted bundles of nanofibrils is the origin of the excellent mechanical strength of the *B. mori* silk [2,3]. As the major component of *B. mori* silk, the primary structure of silk fibroin consists of H-L chain blocks of hydrophobic heavy chains (H-fibroin, approximately 391 kDa) and hydrophilic light chains (L-chain, approximately 26 kDa) linked together by disulfide bonds and glycoprotein P25 (approximately 25.2 kDa) tied to the H-L chain blocks through hydrophobic reactions [5]. The silk fibroin primary structure can assume various secondary structural forms, including α -helices, random coils, β -pleated sheets, and β -turns. The hydrophobic H-fibroin domains form anti-parallel β -sheet crystalline structures, imparting strength and stiffness, whereas the hydrophilic light chain domains form the less ordered, poorly oriented amorphous matrix adopting random coils, β -turns, or α -helix structures, allowing elasticity (Figure 1d). The abundance of these secondary structures of silk fibroin endows it with a unique hierarchical structure that determines its stability and drives its final properties [6,7].

Figure 1. Overview of the origin and structures of silk fibroin. (a) Popular silk sources (1. *Nephila clavipes* spiders, 2. *Araneus diadematus* spiders, 3. *Antherea pernyi* wildsilk worms, 4. *Samia cynthia ricini* wildsilk worms, 5. *B. mori* domestic silkworms). (Reproduced from [2]. CC BY 4.0.). (b) *B. mori* silkworm and cocoons (Reproduced from [2]. CC BY 4.0.). (c) Composition of *B. mori* silk (Reproduced with permission [8]. Copyright 2018, The Royal Society of Chemistry). (d) Hierarchical structure of *B. mori* silk fibroin [9,10] (Reproduced with permission [9]. Copyright 2014, John Wiley and Sons; Reproduced from [10]. CC BY 4.0.).

Conventionally, sericin is removed by a process known as degumming with only silk fibroin left for industrial applications because it has improved mechanical properties, luster, and soft-handling than the raw silk [11]. Due to its hierarchical structure and versatility, the utilization of *B. mori* silk fibroin has extended from the textile industry to various high-tech applications in the form of multiple regenerated *B. mori* silk fibroin material formats. Inspired by the ability of *B. mori* silkworms to synthesize and store liquid silk, researchers have attempted to use the top-down approach to reverse *B. mori* silk fibroin filament into solution then to solidify into versatile forms such as fibers, particles, films, hydrogels, and three dimensional (3D) materials for multiple applications such as wearable electronic devices, photonic devices, water ultrafiltration systems, biosensors, drug delivery systems, and tissue engineering [12,13]. The purpose of this review is to provide an overview of recent progress in the development of regenerated *B. mori* silk fibroin materials for diverse applications. Reverse engineered silk fibroin extraction methods are first introduced, and then recent advances in extraction techniques are discussed. Fabrication methods of regenerated silk fibroin materials in various formats are also addressed in detail, and in particular, progress in new fabrication technologies is presented. Attractive applications of either pure or composite regenerated silk fibroin materials are then summarized and highlighted. The challenges faced by current approaches in the production of regenerated silk fibroin materials and future directions acquired for pushing these favorable materials further toward the above-mentioned applications are further elaborated.

2. Reverse engineered *B. mori* silk fibroin extraction

Despite various silk fibroin-based materials regeneration methods, a two-step silk fibroin extraction process including degumming and dissolving is essential.

2.1. Degumming of raw silk

Silk degumming is the process by which the gummy layer of sericin, which binds two fibroin filaments, is removed by breaking peptide bonds present between sericin and fibroin through thermochemical treatment of cocoons or raw silk. It has been reported that sericin can cause allergic reactions and infections in humans and inhibit the premature conversion of soluble silk (silk I) into gelated and β -sheet silk conformations [14]. Therefore, it is necessary to eliminate sericin and other impurities for better utilization of the silk. Conventional degumming is based on using boiling water or aqueous solutions containing soap, alkaline, acid, enzyme, or amine to hydrolyze the sericin (Figure 2) [15]. Comparative analysis of various degumming methods is provided in Table 1.

Water degumming is a green processing method and the cheapest one involving no use of chemicals. However, high temperature, long and repeated processing times, and pressure are always required for efficient removal of sericin. Besides, it is reported that water degumming has the possibility of causing silk fibroin damage at such high temperature for long time, and the problem of incomplete degumming. Thus, this process is not commercially adopted. Water degumming

Figure 2. Degumming routes of silk fibers.

is commonly used to soften and partially dissolve sericin by soaking cocoons into water with a temperature of 50–60 °C to enable the silk filament unwinding in silk reeling in the textile industry [16].

Soap degumming involving treating silk with a slightly alkaline soap solution is one of the most commonly used method. Various sodium-based soap, such as sodium stearate, sodium myristate, sodium laurate, sodium arachidate, sodium oleate, sodium ricinoleate, and sodium caprylate, based on distinct oils such as olive oil, palm oil, coconut oil, laurel oil, canola oil, palm kernel oil, and tallow oil have been employed for soap degumming purposes. The removal of sericin by soap solutions is due to alkali formation upon soap hydrolysis, which forms chemical bonds with sericin and turns it into soluble soda salt. Therefore, soaps with greater hydrolysis capacity perform more effective degumming. The degumming effect of soap-based treatment is also influenced by parameters such as temperature, degumming time, liquor ratio, and pH of solution. Generally, the quantity of soap, degumming temperature, degumming time, liquor ratio, and pH required with the soap solution may approximately take the values of 20%–30% soap to the weight of material, 90–95 °C, 1.5–2 h, 30–40:1, 9.7–10.5, respectively. Though the soap degumming method has advantages of mild processing, avoidance of over-degumming, and increasing the softness, whiteness, absorbency, and luster properties of the resultant fibroin fibers, the load of soap in the solution is high, and it is susceptible to hard water. In order to avoid metallic complex deposits and resulting stains, the water should be properly softened [17–19].

Alkali degumming is another most commonly used method both in industry and laboratory since it's beneficial both on economic and quality grounds. Various alkalis, including sodium carbonate (Na_2CO_3), sodium bicarbonate (NaHCO_3), sodium hydroxide (NaOH), potassium carbonate (KCO_3), sodium silicate ($\text{Na}_{2x}\text{SiO}_{2y+x}$), sodium pyrophosphate ($\text{Na}_4\text{P}_2\text{O}_7$), trisodium phosphate (Na_3PO_4), borax ($\text{Na}_2[\text{B}_4\text{O}_5(\text{OH})_4] \cdot 8\text{H}_2\text{O}$), and ammonia (NH_3), have been investigated for use as degumming agents. Desired pH and appropriate concentration of the alkali solution is important for achieving high degumming efficiency and not causing injury to the silk fibroin. However, alkalis are always used in combination with soap or detergents, because it leaves the resultant fibers a dirty yellowish color and harsh appearance when used alone for degumming [20, 21].

Degumming of silk using dilute acid, such as tartaric acid, lactic acid, oxalic acid, citric acid, succinic acid, malonic acid, trichloroacetic acid, monochloroacetic acid, glacial acetic acid, and sulfuric acid, is an approach that has long been practiced. Effective acid degumming occurs in the pH range of 1.5–2. These dilute acids specifically perform a hydrolytic attack on sericin protein to break peptide bonds between aspartic acid and glutamic acid. Acid degumming provides very fast degumming rate and avoids the use of high temperature. However acid degumming is used less due to the fact that alkaline solution is safer for fibroin than acids [22, 23].

Degumming of silk by enzymes such as trypsin, papain, and bacterial enzymes is also a method that has long been practiced. The mechanism of enzymatic degumming is that the proteolytic enzymes cleave the peptide and amide linkages of sericin and convert them into amino acid. Different enzymes show effective degumming at different pH. Compare this with nonspecific hydrolytic reactions of other methods: studies have indicated that proteolytic enzymes react only at specific sites. Since degumming by this method is generally carried out at comparatively low temperatures ranging from 37 °C to 60 °C under mildly alkaline or acid conditions, enzymatically degummed silk fibers are less damaged with a higher degree of surface whiteness and soft handle compared with soap- or alkali-treated silk fibers. The disadvantage of this method is that hydrophobic impurities such as natural wax, twisting oil, and sericin cannot be completely removed due to the mild processing conditions. Moreover, it is unsuitable for large-scale use due to its low efficiency [24, 25].

Organic amines such as methylamine, ethylamine, diethylamine, and triethylamine have also been investigated as alternatives degumming agents to optimize the degumming conditions. The mechanism of amine degumming is similar to that of alkalis, since sericin removal from silk fibers by this method is associated with the fact that amines ionize in water to give hydroxyl (OH) ions. Reports have shown that under optimized conditions amine degumming shows a degumming effect comparable with Marseilles soap degumming but that was less susceptible to the hardness of water. The disadvantage of this method is that gradual removal of sericin leads to a low degumming rate [26, 27].

Until now, water treatment has been used to soften and partially dissolve sericin to enable the silk filament unwinding in silk reeling in textile industry. Na_2CO_3 is the most highly preferred

Table 1. Comparative study of different silk degumming methods.

Degumming method	Degumming reagents	Degumming mechanism	Advantage	Disadvantage	References
Water	Water	Hydrolysis of sericin	Green, cheap	High temperature, pressure, low degumming rate, incomplete degumming	16
Soap	Marseille, sodium laurate, sodium myristate, sodium stearate, etc.	Alkali formed upon on soap hydrolysis breaks peptide bonds of sericin	Mild processing	Very expensive, time consuming, energy-inefficient, susceptible to hard water	17–19
Alkali	Na_2CO_3 , NaHCO_3 , NaOH , KCO_3 , Na_2SiO_3 , $\text{Na}_4\text{P}_2\text{O}_7$, Na_3PO_4 , NH_3 , etc.	Alkali breaks nonspecific peptide bonds	Low cost, high efficiency	Imparts yellowish color to the degummed fibers when used alone, susceptible to hard water	20, 21
Acid	Tartaric acid, citric acid, oxalic acid, lactic acid, glacial acetic acid, etc.	Hydrolytic attack on peptide bonds	Fast degumming, heat and time saving	May cause injury to degummed fibers	22, 23
Enzyme	Trypsin, papain, proteases, etc.	Catalyzes hydrolytic attack on peptide bonds	Low input energy, no hazardous chemical pollution, mild processing	Unable to remove hydrophobic impurities completely	24, 25
Amine	Methylamine, ethylamine, diethylamine, triethylamine, etc.	Hydrolysis of peptide linkages between sericin and fibroin in alkaline pH	Gives uniform and undamaged silk fibers (not affected by hard water)	Low degumming rate	26, 27

and the most common agent adopted in laboratory processes [11, 28]. Soda made from $\text{Na}_2\text{CO}_3/\text{NaHCO}_3$ is the most widely used alkali to be mixed with soap or detergents for degumming in industry [29, 30]. The degumming waste solution using this method not only contains a large quantity of sericin, but also includes chemicals of alkalis, soap, and so on. Thus, concerns for environmental protection and sustainability of resources have prompted researchers to explore green, clean, and facile degumming methods to obtain uniform, undamaged degummed silk fibers with improved properties. Research with different focuses can mainly be divided into three categories, using new greener degumming agents, using new energy, and improving the conventional degumming methods in a green way. For example, Wang et al. synthesized a biodegradable amino acid-type anionic surfactant with amino acids of silk fibroin and lauroyl chloride for silk degumming. They studied it systematically in comparison with the traditional degumming methods such as Na_2CO_3 and neutral soap. The experimental results showed that the degumming effect of the developed new silk protein surfactant was comparable to neutral soap and far superior to Na_2CO_3 , and the degumming waste liquid is easily decomposed by microbes [31]. Other greener degumming reagents such as $\text{Ca}(\text{OH})_2$ [32], halotolerant metalloprotease isolated from metabolites of *Vibrio* sp. LA-05 [33], an enzyme from natural sources such as papaya skin, pineapple skin and guava leaf [34], protease from *Bacillus* sp. C4 [35], hydrated lime water [36], and alkyl polyglycoside [37] have been explored for treatment. Microwave-assisted silk degumming was carried out by Haggag et al. [38] and Mahmoodi et al. [39]. Gupta et al. employed infrared heating as an approach for sericin removal and compared the result with that of the conventional high temperature high pressure (HTHP) process. Their results showed that complete removal of sericin could be achieved by using a lower temperature, lower time of treatment and lesser water consumption as compared with the HTHP process [40]. Vyas et al. [41] and Cai et al. [42] performed ultrasonication-assisted silk degumming treatment in the presence of different degumming agents. This method has the advantages of short processing time and uniform degummed silk fibers. Lo et al. tried a recyclable, lower water consumption, and lower energy consumption method to degum silk by using CO_2 supercritical fluid under acidic condition. Their results showed that the quality of silk fibroin degummed by CO_2 supercritical fluid was found to be better when compared with the silk degummed by NH_4OH . The CO_2 emission can be removed and reused for the next degumming procedure [43]. Cao et al. synthesized

strongly alkaline electrolyzed water (SAEW) with a pH of 11.5 as a degumming agent by electrolyzing tap water with a laboratory-made combined water electrolyzer. The hardness of SAEW was found to be 30% less than that of the tap water, whereas the concentrations of Na^+ in SAEW were 18% higher than those in the tap water. Their results showed that there was no evident difference among the surface properties of silk fibroin degummed by SAEW, Na_2CO_3 and neutral soap degumming methods (Figure 3) [44]. Wang et al. performed pressurized steam treatment on raw silk to remove sericin. It was found that steam treatment with lower pressure (0.14 MPa) and long residence time (90 min) generates no adverse effects on the physicochemical properties of the degummed silk fibers [45].

2.2. Dissolving of degummed silk

Dissolving of the degummed silk is the next step followed by degumming of silk. Either aqueous or nonaqueous silk fibroin solution can be obtained from which a range of silk fibroin-based materials in versatile formats can be fabricated [46, 47]. Table 2 provides commonly used methods for dissolving degummed silk.

An aqueous silk fibroin solution is the most commonly utilized reverse engineered silk fibroin solution for generation of many different silk fibroin formats [46]. The common strategy for the preparation of aqueous silk fibroin solution is the dissolution of degummed silk in inorganic salt systems. Among all solvents, the two most widely used solvent systems for dissolving include the highly concentrated aqueous LiBr solution and the ternary solvent system based on $\text{CaCl}_2/\text{CH}_3\text{CH}_2\text{OH}/\text{H}_2\text{O}$ with 1/8/2 molar ratio. Other inorganic salt systems including $\text{Ca}(\text{NO}_3)_2/\text{CH}_3\text{OH}$, LiSCN, NaSCN, and ZnCl_2 are also employed [47, 48]. The dissolving of silk fibroin in inorganic salt systems is due to hydrogen bond disruption in the crystalline structure (ordered, hydrophobic, and high-density β sheet region). It is worth noting that the dissolved silk fibroin salt solution requires extensive dialysis and concentration before the regenerated silk fibroin is suitable for use. The concentration process is normally done by dialysis against an aqueous polyethylene glycol solution (20 wt%) to extract water [15, 46, 47]. Sometimes freeze-drying followed by redissolving at required concentration is needed. Thus, the whole dissolving, dialysis, concentration, and freeze-drying processes for extraction of regenerated silk fibroin are time-consuming [4]. In addition, the regenerated silk

Figure 3. Surface images of single filament of silk fibroin degummed from different degumming methods. (a) Neutral soap, (b) SAEW, (c) Na_2CO_3 . (Reproduced from [44]. CC BY 3.0.).

Table 2. Methods for dissolving degummed silk

Types of silk fibroin solution	Dissolving agents	Dissolving mechanism	Followed processing steps	Advantage	Disadvantage	References
Aqueous	Inorganic aqueous solutions: LiBr, CaCl ₂ :EtOH:H ₂ O with 1:8:2 molar ratio solvent system, etc.	Destroy hydrogen bonds in the crystalline structure to promote solubility	Dialysis or concentration/ freeze-drying	Mild processing conditions to preserve the activity of biologics.	Complex, time- and man power-consuming, short half-life	4, 15, 46,47, 48
Non-aqueous	Organic solvents: Hexafluoro-2-propanol (HFIP), formic acid, formic acid/CaCl ₂ , hexafluoroacetone (HFA) Ionic liquids: NMMO, AMIMCl, BMIMCl, BMIMAc, EMIMCl, BMIMBr, BMIMI, etc.					
				Simple, efficient	Degradation of the protein, toxic, expensive, extremely corrosive	46, 47, 49, 50, 51

fibroin solution is very unstable and easily denatured and can aggregate to a gel state very easily [46, 47].

Nonaqueous silk fibroin solution primarily used for producing regenerated fibers and films via wet spinning, dry spinning, and electrospinning. The most commonly used solvents for artificial spinning are hexafluoro-2-propanol (HFIP), hexafluoroacetone (HFA), formic acid, and formic acid/CaCl₂ [47, 49, 50]. These solvents first cause decomposition of the hydrogen bonds and then break down the peptide bonds. However, these solvents are strongly corrosive, toxic, and volatile. And the obtained silk fibroin solution is not conducive to preservation. Ecofriendly solvents such as N-Methylmorpholine N-oxide (NMMO) and ionic liquids such as 1-Allyl-3-methylimidazolium chloride (AMIMCl), 1-Butyl-3-methylimidazolium chloride (BMIMCl), 1-Butyl-3-methylimidazole acetate (BMIMAc), 1-Ethyl-3-methylimidazolium chloride (EMIMCl), 1-Butyl-3-methylimidazolium bromide (BMIMBr), 1-Butyl-3-methylimidazolium iodide (BMIMI), etc. have also been explored for dissolving. Compared with the organic solvents or inorganic salt solvents, dissolution in ionic liquids has the advantages of simple, rapid, and greener preparation processes; stable solutions; elimination of the use of toxic organic volatile liquids; and convenient recycling. However, dissolution in ionic liquid needs high temperatures, which can lead to the degradation of silk protein [46, 47, 50, 51].

Recently, Wang et al. proposed a green and environment-friendly method to enhance efficiency of aqueous silk fibroin solution preparation. In particular, they used excess acetone to extract concentrated silk fibroin-LiBr solution for dialysis. The required dialysis time can be reduced by half using this method. It was found that the stability, peptide chains, and secondary structure of regenerated silk fibroin are minimally changed. In addition, the resulting acetone and salt in wastewater can be easily separated and recycled for silk fibroin regeneration [52]. Yet, it can be seen that the extraction of regenerated silk fibroin with only mild degradation and stable β -sheet conformation in large scale by cost effective and easy methods is still a problem.

3. B. *mori* silk fibroin materials fabrication

After researchers successfully obtain the silk solution, the regeneration of silk fibroin into novel material formats such as fibers, particles, films, hydrogels, and 3D materials with different morphologies can be done, according to the type of end-application (Figure 4).

In comparison with natural silk fiber, regenerated silk fibers can be prepared by wet spinning, dry spinning, and electrospinning. Generally, silk fibroin solution used for artificial spinning is primarily nonaqueous silk fibroin dissolved with organic solvents or ionic liquids because of the better rheological properties of the solution and better evaporation of the solvent [46, 47]. In wet spinning, the silk protein solution is extruded through a spinneret directly into a coagulation bath that initiates solidification into fibers via precipitation. In contrast, dry spinning solidification of the fiber occurs due to the evaporation of a volatile solvent [59]. Electrospinning is a simple and

Figure 4. Basic structures of silk fibroin-based materials include (a) regenerated silk fibroin fiber by wet spinning (Reproduced from [53]. CC BY 4.0.), (b) silk fibroin nanofibers by electrospinning (Reproduced from [54]. CC BY 4.0.), (c) silk fibroin nanoparticles (Reproduced with permission [55]. Copyright 2020, John Wiley and Sons), (d) silk fibroin film (Reproduced from [56]. CC BY 4.0.), (e) silk fibroin hydrogel (Reproduced from [57]. CC BY 4.0.), and (f) silk fibroin 3D sponge (Reproduced from [58]. CC BY 3.0.).

useful technique for producing nano/micro fibers possessing large surface areas. By these artificial spinning processes, the diameter, morphology, and mechanical properties of the regenerated silk fibroin fibers obtained can be conveniently modified. Moreover, the regenerated silk fibroin fibers can be endowed with diverse optical, electrical, and biofunctional properties by the addition of various functional fillers during fabrication [60]. For example, Ma et al. fabricated photochromic regenerated silk fibroin/Tungsten trioxide nanoparticles hybrid fibers via wet spinning process [60]. Mohsen et al. fabricated short staple microfibers based on chitosan or silk fibroin via the wet spinning technique to adsorb hexavalent chromium from aqueous solution [61]. Mostafavi et al. fabricated vitamin D-loaded silk fibroin/polycaprolactone (SF/PCL) nanofibrous scaffolds for bone tissue engineering applications [62]. Besides these conventional processes, straining flow spinning recently appears as a versatile and robust technique that allows efficient spinning of regenerated silk fibers. Geometrical and hydrodynamic processing parameters can be integrated into this technique, which allows spinning under a much wider range of chemistries [63]. Liquid exfoliation, which directly exfoliates silk nanofibrils from degummed silk fibers, is another newly developed method that can preserve the native structural elements and features of silk fibers with the aim to rearrange them at the nanofibril level for enhanced properties [64, 65].

Silk fibroin particles can be fabricated by either the top-down method or the bottom-up method. The top-down method involves simply chopping, grinding, and crushing the SF degummed fibers into smaller aggregates. This method generally results in big nanoparticle aggregates with a wide size range and needs a long time and specific apparatus [8, 46]. The bottom-up method uses the silk fibroin solution as the starting material. Broad bottom up-methods such as self-assembly, freeze-drying, and grinding, freeze-thawing, spray-drying, jet-breaking, electro-spraying, microfluidic technique, dissolution, and salting out are applied to produce silk fibroin particles [8, 66]. The self-assembly method takes advantage of silk fibroin self-assembly behavior ruled by hydrophilic and hydrophobic chain interactions. For example, Xiao et al. fabricated regenerated silk fibroin microsphere-embedded Fe_3O_4 magnetic nanoparticles for immobilization of zymolyase through a controllable ethanol-induced interface self-assembly. The prepared microsphere exhibited high immobilization efficiency [67]. Spray-drying, jet-breaking, and electro-spraying are similar technologies, which involve the breaking down of the aqueous silk fibroin flow into small droplets by force [8, 68]. Dissolution represents the most common method for obtaining silk fibroin particles. It is based on the reduction of the silk fibroin chain solubility in the presence of organic solvents such as acetone, ethanol, dimethyl sulfoxide (DMSO), and methanol, leading to phase separation [69, 70]. Salting out is another approach employed for the production of silk fibroin

particles. The formation of particles results from the increased hydrophobic interaction between the SF protein chains due to the dehydration effect of the added salt ions. The manipulation of the solution pH has been found to have a profound effect on the silk secondary structure, zeta potential, as well as salting out efficiency [59].

Silk fibroin films can be easily prepared by solution casting, spin-coating, or layer-by-layer deposition methods [2, 14]. Water insoluble and flexible silk fibroin films can be fabricated by adjustment of β -sheet content in the films via controlled drying, water annealing, stretching, and organic solvents treatment [56, 62]. Wang et al. fabricated silk fibroin films with tunable ductility and porosity by adjusting the protein self-assembly process through combinations with glycerol and polyethylene glycol 400 and regulating the film-casting temperature. Among various conditions screened, the composite film with a mass ratio of silk fibroin/polyethylene glycol 400/glycerol of 10:5:3 prepared at 4°C exhibited remarkable ductility with a tensile strength of 2.7 ± 0.2 MPa and an elongation at the break of $164.24 \pm 24.20\%$ [71]. Silk films with micro/nano-scale patterned morphology can be prepared by the nanolithography technology including soft-lithography, photolithography, ion beam lithography, and nanoimprinting. Micro/nano-scale patterned silk fibroin films have the potential being explored for guided cell growth and as optical storage medium [72, 73]. Soft-lithography involves casting the aqueous silk fibroin solution on nanostructured surfaces made from elastomeric molds such as polydimethylsiloxane (PDMS) [74]. Ion beam lithography uses an accelerated beam of ions to create nanostructures on cure silk fibroin films [75]. Photolithography is an efficient and cost-effective technique that uses light to define patterns on cure silk fibroin films [76].

Silk fibroin hydrogels can be prepared through sol-gel transition of fibroin aqueous solution triggered by physical or chemical processes, where a molecular network forms by controlling the formation of β -sheet structures as crosslinks for silk [14, 59]. Physically crosslinked silk fibroin hydrogels can be produced by temperature control, application of shear force, ultrasonication, and electrical current, etc. The underlying mechanism of this process is the self-assembly of proteins via enhanced hydrophobic interactions. Chemically crosslinked silk fibroin hydrogels can be produced by pH control; addition of precipitating agents such as concentrated salt solutions, organic solvents, surface agents, large polymeric precipitating agents, and small neutral additives; chemical stabilization; and chemical modification. Generally, a lower pH and a higher incubation temperature facilitate increased kinetics toward the sol-gel transition [77, 78]. In addition to the above-mentioned methods, Hasturk et al. recently fabricated silk-gelatin hydrogel scaffold with tunable gelation kinetics, mechanical properties and bioactivity for cell culture and encapsulation via enzymatic crosslinking [79]. Marín et al. synthesized composite hydrogel of regenerated silk fibroin incorporating gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), or iron oxide nanoparticles (IONPs) using bisphosphonate-decorated nanoparticles (NPs) to prevent their aggregation and enzyme-assisted cross-linking method to control the formation of the

silk fibroin composite hydrogels in the presence of the NPs [80]. Confined alignment is another new method used to fabricate silk fibroin hydrogel with controlled molecular alignment and degree of crystallinity. This method enables the design and engineering of biopolymer-based materials with controlled hierarchical structure at multiple length scales and tunable properties [81].

Various forms of silk fibroin-based 3D materials such as porous scaffolds, sponges, foams, tubes, rods, and screws can be fabricated by several most widely adopt techniques including salt-leaching, gas foaming, freeze-drying, and electrospinning. In the salt-leaching method, salts are added to the silk fibroin solution, the mixture is then placed in a mold. After the mixture solution turns into gel, the salt is removed by immersing the mixture in water to obtain the salt-free 3D porous scaffolds. However, one major issue with this method is that the leaching of salt particles can lead to poor interconnection and abnormal pore shape. Gas foaming is a kind of method to create an interconnected pore structure with high porosity by rapid pressure relief around the liquefied polymer. Pore structure and porosity of the fabricated constructs can be tuned by varying the amount of gas in polymer. Freeze-drying is an important means to fabricate silk fibroin-based porous sponge scaffolds. The pore size and microstructures can be effectively controlled by adjusting the freezing temperature or silk fibroin concentration. Moreover, aligned scaffolds can be obtained by controlling the frozen conditions [2, 3, 82–85]. Besides these conventionally used methods, Guo et al. recently fabricated silk fibroin-based bulk materials including bars, rods, plates, tubes with caps, and screws with tunable mechanical properties via thermal processing for medical device applications. Specifically, amorphous silk nanomaterials reconstructed from the LiBr-silk fibroin solution were first produced, which were then processed into robust structural materials by hot pressing [86]. The method of 3D printing is also new, allowing the formation of silk fibroin-based 3D materials with biologically relevant structures in defined geometries with microscale resolution that are difficult or impossible to manufacture with conventional fabrication techniques. Based on the use of different silk fibroin solution inks such as the pure aqueous silk fibroin solution, 3D printing uses a silk fibroin solution incorporated with biologically active molecules and dopants, a self-curing silk fibroin solution, and a silk fibroin solution incorporated with living cells; and 3D printing in combination with sacrificial templating has been developed to fabricate 3D silk fibroin materials with complex structures down to the microscale (Figure 5) [87–91].

4. B. *mori* silk fibroin materials applications

Attractive properties including light weight, excellent mechanical property, flexibility, optical transparency, thermal stability, biocompatibility, controllable biodegradability, and versatility of silk fibroin along with progress in biomedicine and nanofabrication technologies have expanded the scope of functionalized silk fibroin-based materials applications to medical, electronic, optical, and filtration applications.

Figure 5. Digital light processing 3D printed silk fibroin hydrogel for tissue engineering. (a) Modification of silk fibroin molecule with glycidyl methacrylate (GMA). (b) Reaction process for the photopolymerization of Sil-MA in the presence of LAP photoinitiator and 3D structure of Sil-MA hydrogel formed via digital light process (DLP) printing. (c) CAD images and printed images of ear and brain. (Reproduced from [91]. CC BY 4.0.).

4.1. Biomedical applications

In the biomedical field, current routine clinical uses of silk fibroin, working directly with the degummed silk fiber, include silk surgical mesh for abdominal wall reconstruction and investigative plastic surgery applications, silk fabrics for the treatment of dermatological conditions, and silk sutures for use in general soft tissue approximating ligation. Present clinical trials using regenerated silk fibroin materials include water-resistant silk films for wound healing and thin silk films for acute and chronic tympanic membrane perforation repair [5]. In addition to these routine clinical uses and clinical trials, regenerated silk fibroin-based materials in a wide spectrum of formats have been investigated as tissue engineering scaffolds and drug carriers in biomedical applications in preclinical studies. Until now, SF has been fabricated in a variety of materials such

as nanofibrous mats, hydrogels, and 3D porous scaffolds for use in the engineering and regeneration of a variety of tissues including skin, nerves, tendons, blood vessels, bone, cartilage, ligaments, and tendon (Table 3).

Electrospun silk fibroin nonwoven mats consisting of nanofibers are remarkable tissue engineering materials since their extracellular matrix (ECM)-like fibrous nature is suitable for cell interaction (Figure 6a) [92]. And functional silk fibroin nanofibrous mats can be fabricated by the incorporation of growth factors or other signaling factors [62,96]. By controlling the gelation process (Figure 6b), blending with other biopolymers (Figure 6c) and incorporating biologically functional moieties (Figure 6d), silk fibroin hydrogels or sponges with fine-tuned stiffness and optimized cell functions can be constructed for specialized tissue engineering applications [93–95]. Besides mainly being

Table 3. List of tissue-engineered materials based on silk fibroin

Material formats	Type of tissue engineered	Preparation methods	References
Tube	Vascular graft	Electrospinning	92
Hydrogel	Cartilage tissue	Bioprinting or freeze-drying	93,94
Sponge	Bone tissue	Freeze-drying	95
Nanofibrous mat	Skin tissue	Electrospinning	96
Cylindrical scaffold	Nerve	Freezing-induced assembly	97
Cylindrical scaffold	Tendon/ligament-to-bone tissue	Controlled freeze-drying	98
The collagen sponge permeated into the rings of knitted silk mesh.	Anterior cruciate ligament	Knitting and freeze-drying	99

used as injectable tissue fillers, silk fibroin hydrogels with finely tuned properties can also be used for hard tissue regeneration [79, 80, 94]. Silk fibroin 3D biodegradable scaffolds taking the role of ECM analogues can serve as a necessary template or matrix supporting cell attachment, proliferation, differentiation, tissue neogenesis, formation of a new extracellular matrix, and transportation of nutrients and metabolic wastes [83–85, 94, 95, 98, 99]. It is worth noting that each type of engineered tissue should possess the correct balance of structural features and biological and mechanical properties for the induction of the desired cellular activity and to guide appropriate tissue regeneration.

Due to their combination of robust mechanical properties, controllable biodegradability and drug stabilization effect, silk fibroin-based materials have been investigated as sustainable drug delivery vehicles for a wide range of biological molecules including proteins, growth factors, peptides, and gene and therapeutic drugs such as anticancer agents and small molecule drugs [2, 66, 77]. Silk fibroin-based materials in the format of nanoparticles, electrospun nanofibrous mats, hydrogels, aerogels, coatings, and microneedles have been implemented as drug delivery platforms. Silk fibroin-based nanoparticles have been investigated as drug carriers due to their high binding capacity for various drugs, controlled drug release properties and mild preparation conditions.

Figure 6. Schematic diagram of the silk fibroin-based materials for tissue engineering. (a) Small-diameter silk fibroin vascular grafts. (Reproduced from [92]. CC BY 4.0.). (b) 3D printed silk-gelatin hydrogel scaffold for cartilage regeneration. (Reproduced from [93]. CC BY 4.0.). (c) Bacterial cellulose/silk fibroin double network hydrogel for artificial cartilage. (Reproduced with permission [94]. Copyright 2019, Springer Nature B.V.). (d) Three-dimensional porous silk fibroin/graphene oxide scaffold. (Reproduced with permission [95]. Copyright 2019, Springer Nature B.V.).

By developing green synthesis methods and adjusting the particle size, the chemical structure, and properties, modified or recombinant nontoxic silk fibroin-based nanoparticles can be designed to improve the therapeutic efficiency of drugs encapsulated into these nanoparticles [100–104]. Silk fibroin-based nanofibrous mats have been used as potential carriers for drug delivery due to higher drug encapsulation efficiency and better stability than other drug formulations. By manipulating the crystallinity and biodegradation rate of silk fibroin via functionalization and optimizing the porosity, morphology, and diameter of nanofibers, silk fibroin-based nanofibrous mats with controlled drug release and enhanced cell behaviors can be obtained (Figure 7a) [105]. Moreover, high porosity and good interconnectivity between the pores of electrospun nanofibrous mats make them suitable for use as mass transporters [106]. Silk fibroin hydrogel, with a microenvironment similar to the ECM, is often used as a drug carrier due to its high affinity to these drugs and its molecular permeability. Research has been focused on fabrication of silk fibroin-based composite hydrogels with tuned properties, stimuli responsiveness, and optimized treatment effect. Niu et al. fabricated a newer type of drug releasing enzymatically crosslinked hydrogel based on a semi-interpenetrating network of silk fibroin and poly(vinyl alcohol) (PVA) (Figure 7b). The fabricated composite hydrogel was found to possess lamellar structure and release properties [107]. Akrami-Hasan-Kohal, et al. fabricated a sonication-assisted cross-linking silk fibroin hydrogel/dexamethasone sodium phosphate loaded chitosan nanoparticles with ideal physical properties and long-term drug release [108]. Silk fibroin-based films and porous scaffolds such as aerogels have also been used as drug carriers because of their open-pore network and structure tenability. The porosity and surface area of the device may affect its drug release kinetics [109–111]. Silk fibroin coatings have also been combined with liposomes for long-term and targeted drug delivery (Figure 7c) [112, 113]. Due to its unique combination of favorable mechanical strength and ability to maintain the activity of encapsulated bioactive factors, the silk fibroin-based microneedles have been explored as a

minimally invasive platform for delivering drugs or vaccines in a more patient-friendly manner. For example, Shin et al. fabricated oblique and sharp silk fibroin microneedles by digital light processing 3D printing for controllable transdermal drug delivery. The fabricated microneedles can realize effective transdermal delivery and controllable release of drug molecules [114]. Drug delivery devices made of silk fibroin may be found in a variety of material formats. Their choice depends on the mode of application, processability, desired release kinetics, and stability of the drug. Facile and green strategies should be developed to fabricate nontoxic silk fibroin-based materials with tunable properties and stimuli responsiveness for effective drug release.

4.2. Electronic applications

Flexible electronic devices are necessary for applications involving unconventional interfaces, such as soft and curved biological systems, where traditional silicon-based electronics present a mechanical mismatch [115]. By virtue of its light weight; excellent mechanical, dielectric, and optical properties; superior biosustainability and biodegradability; and ease of fabrication, silk fibroin has been utilized as the active element in the design of high-performance flexible electronics devices for a wide range of applications (Figure 8).

Silk fibroin has been combined with conductive materials such as carbon materials, ionic liquid, conducting polymers, and metal nanowires for sensor, electronic storage devices, electrodes, polymer electrolytes, and transient electronics applications, as listed in Table 4.

Although silk fibroin can be used as passive substrates and dielectric layers in electronic devices, the incorporated conductive components limited their biodegradability and bioresorbability for applications in biological systems [13, 115].

Table 4. List of flexible electronic devices based on silk fibroin materials

Material formats	Potential applications	Working mechanism	References
Silk fibroin/graphene film	Humidity sensor	Water content in the film causes change in resistance	116
MXene coated silk fibroin nanofiber membrane and MXene ink-printed silk fibroin interdigitated electrode	Medical pressure sensor	Resistance change upon pressure	117
Silk fibroin hydrogel ionotronics	Environmental monitoring and communications	Resistance change upon temperature and/or humidity change	118
Soft conductive hydrogel	Strain/pressure sensors and triboelectric nanogenerators	Strain or pressure causes change in resistance	119
Flexible silk nanofiber/single-wall carbon nanotube composite film	Electronic-storage device	Electric heating behavior	120
Silk fibroin-based film	Electrolytes	Ionic conductivity	121

Figure 7. Schematic diagram of the silk fibroin-based materials for drug release. (a) Dual-drug-loaded SF/PLGA scaffolds for bone regeneration. (Reproduced from [105]. CC BY 4.0.). (b) PVA/SF enzymatically crosslinked semi-interpenetrating hydrogel for hydrophobic drug delivery. (Reproduced from [107]. CC BY 4.0.). (c) Multi-layered silk fibroin coatings for controlled release of drug. (Reproduced from [112]. CC BY 4.0.).

Figure 8. Schematic diagram of the silk fibroin-based materials for flexible electronics devices. (a) SF/Graphene film-based humidity sensor. (Reproduced from [116]. CC BY 4.0.). (b) MXene/SF nanocomposites-based pressure sensor. (Reproduced with permission [117]. Copyright 2021, American Chemical Society). (c) SF hydrogel ionotronics-based temperature and humidity sensor. (Reproduced from [118]. CC BY 4.0.).

4.3. Optical applications

In addition to applications in electronic devices, silk fibroin has also been heavily investigated as an interesting optical material because of its high transparency and excellent mechanical properties. Silk fibroin has been used in a variety of optical devices, such as optical diffraction-based sensors, optical waveguides, optical gazes, and 3D photonics. For example,

Zhou et al. fabricated a set of bioactive optical diffraction-based sensors microfabricated using functionalized silk fibroin films for optical diffraction-based sensing applications, including hydration sensing, biological concealment, therapeutic treatment, and *in vitro* and *in vivo* drug release monitoring upon degradation. Their work sheds light on a new class of transient optical devices—with specific functionalities—that can physically degrade in the body or disappear in the

Figure 9. Schematic diagram of the silk fibroin-based materials for optical devices. (a) 2D phase-shifting binary diffractive optical element made of regenerated silk fibroin films. (Reproduced with permission [122]. Copyright 2017, John Wiley and Sons). (b) silk fibroin-coated magnesium oxide nanospheres for noninvasive bioimaging applications. (Reproduced from [123]. CC BY 4.0.). (c) silk optical planar waveguide. (Reproduced from [125]. CC BY 4.0.).

environment at prescribed times and at controlled rates (Figure 9a) [122]. Li et al. fabricated silk fibroin-coated magnesium oxide nanospheres for noninvasive bioimaging applications (Figure 9b) [123]. The biocompatibility of waveguide material is important when it needs to interface directly with living cells in biomedical applications. Biocompatible silk fibroin-based optical waveguides have been produced by Santos et al. using direct laser writing and Prajzler using direct depositing (Figure 9c), respectively [124, 125]. Lee et al. fabricated silk fibroin films and patterned them into different nanostructures via tip-enhanced near-field infrared nanolithography for rewritable optical storage medium [73].

4.4 Filtration systems

Among various material formats, materials prepared from electrospun nanofibers have properties such as high surface-to-volume ratio, low pressure drop, and controllable morphology and connectivity, making them attractive for achieving excellent filtering performance. Because of their biocompatibility, biodegradability, and nontoxicity, silk fibroin materials in the form of electrospun nanofibrous mats have also been investigated as filtration systems for water treatment and air filtration. For example, Garrido et al. fabricated electrospun silk fibroin/ZnO mats to remove pesticide residues from water under natural sunlight [126]. Zhou et al. fabricated a silk fibroin-graphene oxide functionalized melamine sponge for efficient oil absorption and oil and water separation [127]. Wang, et al. fabricated porous ZnS and ZnO films using silk fibroin as a template by coaxial electrospinning for highly efficient photodegradation of organic dyes (Figure 10a) [128]. Gao et al., [129] Min et al., [130] respectively fabricated electrospun

silk nanofibers for efficient PM 2.5 and submicron particles capture (Figure 10b). Multifunctional silk fibroin nanofiber-based systems showed superior filtration performance with a much lower basis weight compared with commercial filters and absorbents. Yet, further efforts should be devoted to enhance the mechanical properties of the nanofibers for longer life and design more advanced filtration system.

5. Conclusion and outlook

The ubiquity, unique hierarchical structure, light weight, excellent mechanical property, flexibility, optical transparency, thermal stability, biocompatibility, controllable biodegradability, versatility in material format design, and mild aqueous processing of silk fibroin make silk fibroin-based materials an attractive biomaterial for various applications. Great efforts have been made to develop green and facile technologies for reverse-engineered silk fibroin extraction and materials fabrication. Silk fibroin-based materials in versatile formats, including fibers, particles, films, hydrogels, and 3D materials, have been developed for advanced utilities in medical, electronic, optical, and filtration applications. Bio-nanotechnology such as nanoimprinting/patterning, confined alignment, and 3D printing will further provide synergies for the prospective development of silk fibroin-based materials in related applications. Nevertheless, despite the immense level of development of silk fibroin-based materials, challenges in the large-scale production of silk fibroin and the control over the nanostructure of silk fibroin-based materials remain. Most of silk fibroin materials-processing techniques are still time- and solvent-intensive. Better control over the hierarchical

Figure 10. Schematic diagram of the silk fibroin-based materials for filtration systems. (a) Porous ZnS and ZnO films using silk fibroin as a template by coaxial electrospinning for highly efficient photodegradation of organic dyes. (Reproduced with permission [128]. Copyright 2018, John Wiley and Sons). (b) Optically translucent silk nanofibrous air filter. (Reproduced from [130]. CC BY 4.0.)

structure to produce structurally and functionally optimized silk nanomaterials for specific applications is still a problem.

Acknowledgments

This work has been financially supported by the Open Project Program of Key Laboratory of Yarn Materials Forming and Composite Processing Technology (No. MTC2021-04) and the Jiaxing Public Welfare Technology Application Research Project (No. 2021AD10012) of Zhejiang Province. The authors also acknowledge the financial support from the Natural Science Foundation (No. BK20201216), High Education Science Foundation (No. 19KJD540001 & 21KJB540007), and Qinglan Project (No. Jiangsu Teacher 2019-3) of Jiangsu Province. The authors are grateful for the the Open Project Program of Engineering Research Center for Clean Production of Textile Printing and Dyeing, Ministry of Education (No. FZYR2021002 & FZYR2021003).

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